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(71) Applicant: ABBOTT LABORATORIES [US/US]; CHAD 0377/AP6D-2, 100 Abbott Park Road, Abbott Road, IL 60064-6050 (US).

(72) Inventors: WANG, Gary, T.; 8602 Osceola Avenue, Niles, IL 60714 (US). WANG, Sheldon; 14066 Honey Tree Drive, Carmel, IN 46032 (US). GENTLES, Robert; 909 Cali Court, Libertyville, IL 60048 (US).

(74) Agents: ANDERSON, Denton L. et al.; Sheldon & Mak, 225 South Lake Avenue, 9th Floor, Pasadena, CA 91101 (US).

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(54) Title: ARYL PHENYLHETEROCYCLYL SULFIDE DERIVATIVES AND THEIR USE AS CELL ADHESION-INHIBITING ANTI-INFLAMMATORY AND IMMUNE-SUPPRESSIVE AGENTS

(57) Abstract: The present invention relates to novel heterocyclyl-containing diaryl sulfide compounds that are useful for treating inflammatory and immune diseases, to pharmaceutical compositions comprising these compounds, and to methods of inhibiting inflammation or suppressing immune response in a mammal.

ARYL PHENYLHETEROCYCLYL SULFIDE DERIVATIVES AND THEIR USE AS CELL ADHESION-INHIBITING ANTI-INFLAMMATORY AND IMMUNE-SUPPRESSIVE AGENTS

Technical Field

The present invention relates to compounds that are useful for treating inflammatory and immune diseases, to pharmaceutical compositions comprising these compounds, and to methods of inhibiting inflammation or suppressing immune response in a mammal.

Background of the Invention

Inflammation results from a cascade of events that includes vasodilation accompanied by increased vascular permeability and exudation of fluid and plasma proteins. This disruption of vascular integrity precedes or coincides with an infiltration of inflammatory cells. Inflammatory mediators generated at the site of the initial lesion serve to recruit inflammatory cells to the site of injury. These mediators (chemokines such as IL-8, MCP-1, MIP-1, and RANTES, complement fragments and lipid mediators) have chemotactic activity for leukocytes and attract the inflammatory cells to the inflamed lesion. These chemotactic mediators which cause circulating leukocytes to

localize at the site of inflammation require the cells to cross the vascular endothelium at a precise location. This leukocyte recruitment is accomplished by a process called cell adhesion.

Cell adhesion occurs through a coordinately regulated series of steps that allow the leukocytes to first adhere to a specific region of the vascular endothelium and then cross the endothelial barrier to migrate to the inflamed tissue (Springer, T.A., 1994, "Traffic Signals for Lymphocyte Recirculation and Leukocyte Emigration: The Multistep Paradigm", Cell, 76: 301-314; Lawrence, M. B., and Springer, T. A., 1991, "Leukocytes' Roll on a Selectin at Physiologic Flow Rates: Distinction from and Prerequisite for Adhesion Through Integrins", Cell, 65: 859-873; von Adrian, U., Chambers, J. D., McEnvoy, L.M., Bargatze, R.F., Arfos, K.E, and Butcher, E.C., 1991, "Two-Step Model of Leukocyte-Endothelial Cell Interactions in Inflammation", Proc. Nat'l. Acad. Sci. USA, 88: 7538-7542; and Ley, K., Gaehtgens, P., Fennie, C., Singer, M.S., Lasky, L.H. and Rosen, S.D.,1991, "Lectin-Like Cell Adhesion Molecule 1 Mediates Rolling in Mesenteric Venules *in vivo*", Blood, 77: 2553-2555). These steps are mediated by families of adhesion molecules such as integrins, Ig supergene family members, and selectins which are expressed on the surface of the circulating leukocytes and on the vascular endothelial cells. The first step consists of leukocytes rolling along the vascular endothelial cell lining in the region of inflammation. The rolling step is mediated by an interaction between a leukocyte surface oligosaccharide, such as Sialylated Lewis-X antigen (SLe^x), and a selectin molecule expressed on the surface of the endothelial cell in the region of inflammation. The selectin molecule is not normally expressed on the surface of endothelial cells but rather is induced by the action of inflammatory mediators

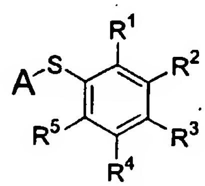
such as TNF-α and interleukin-1. Rolling decreases the velocity of the circulating leukocyte in the region of inflammation and allows the cells to more firmly adhere to the endothelial cell. The firm adhesion is accomplished by the interaction of integrin molecules that are present on the surface of the rolling leukocytes and their counter-receptors (the Ig superfamily molecules) on the surface of the endothelial cell. The Ig superfamily molecules or CAMs (Cell Adhesion Molecules) are either not expressed or are expressed at low levels on normal vascular endothelial cells. The CAM's, like the selectins, are induced by the action of inflammatory mediators like TNF-alpha and IL-1. The final event in the adhesion process is the extravasation of leukocytes through the endothelial cell barrier and their migration along a chemotactic gradient to the site of inflammation. This transmigration is mediated by the conversion of the leukocyte integrin from a low avidity state to a high avidity state. The adhesion process relies on the induced expression of selectins and CAM's on the surface of vascular endothelial cells to mediate the rolling and firm adhesion of leukocytes to the vascular endothelium.

The interaction of the intercellular adhesion molecule ICAM-1 (cd54) on endothelial cells with the integrin LFA-1 on leukocytes plays an important role in endothelial-leukocyte contact. Leukocytes bearing high-affinity LFA-1 adhere to endothelial cells through interaction with ICAM-1, initiating the process of extravasation from the vasculature into the surrounding tissues. Thus, an agent which blocks the ICAM-1/LFA-1 interaction suppresses these early steps in the inflammatory response. Consistent with this background, ICAM-1 knockout mice have numerous abnormalities in their inflammatory responses.

The present invention discloses compounds which bind to the interaction-domain (I-domain) of LFA-1, thus interrupting endothelial cell-leukocyte adhesion by blocking the interaction of LFA-1 with ICAM-1, ICAM-3, and other adhesion molecules. These compounds are useful for the treatment or prophylaxis of diseases in which leukocyte trafficking plays a role, notably acute and chronic inflammatory diseases, autoimmune diseases, tumor metastasis, allograft rejection, and reperfusion injury.

Summary of the Invention

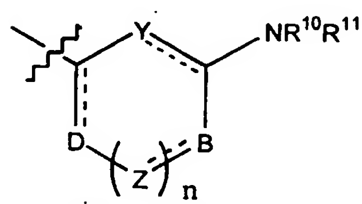
The present invention is directed to compounds of the structure



Formula I

wherein R^1, R^2, R^3, R^4 and R^5 are each independently selected from the group consisting of hydrogen, halogen, alkyl, haloalkyl, alkoxy, cyano, nitro, cycloalkyl and carboxaldehyde;

with the proviso that at least one of R^1 or R^3 is



Formula II

wherein D, B, Y and Z at each occurrence are independently selected from the group consisting of $-CR^6=$, $-CR^7R^8-$, -C(O)-, -O-, $-SO_2-$, -S-,

-N=, and $-NR^9$-;

n is an integer of zero to three;

R^6, R^7, R^8 and R^9, at each occurrence, are each independently selected from the group consisting of hydrogen, alkyl, carboxy, hydroxyalkyl, alkylaminocarbonyl alkyl, dialkylaminocarbonylalkyl and carboxyalkyl; and

R^{10} and R^{11} are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkoxyalkyl, alkoxycarbonylalkyl, carboxyalkyl, hydroxyalkyl, heterocyclyl, heterocyclylalkyl and heterocyclylamino;

wherein R^{10} and R^{11} may be joined to form a three to seven membered heterocyclyl ring, said ring being optionally substituted with one or more substituents R^{13}, wherein R^{13}, at each occurrence is independently selected from the group consisting of alkyl, alkylene, alkoxy, alkoxyalkyl, cycloalkyl, aryl, heterocyclyl, heterocyclylalkyl, heterocyclylcarbonyl, heterocyclylalkylaminocarbonyl, hydroxy, hydroxyalkyl, hydroxyalkoxyalkyl, carboxy, carboxyalkyl, carboxycarbonyl, carboxaldehyde, alkoxycarbonyl, arylalkoxycarbonyl, aminoalkyl, aminoalkanoyl, aminocarbonyl, carboxamido, alkoxycarbonylalkyl, carboxamidoalkyl, cyano, tetrazolyl, alkanoyl, hydroxyalkanoyl, alkanoyloxy, alkanoylamino, alkanoyloxyalkyl, alkanoylaminoalkyl, sulfonate, alkylsulfonyl, alkylsulfonylaminocarbonyl, arylsulfonylaminocarbonyl and heterocyclylsulfonylaminocarbonyl;

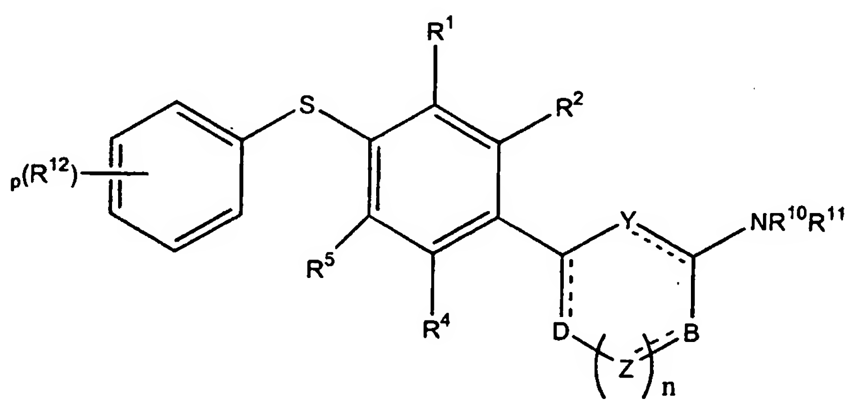
wherein A is an aryl or heterocyclyl group, said aryl or heterocyclyl group having at least one substituent R^{12}, wherein R^{12} is selected from the group consisting of hydrogen, halogen, alkyl, aryl, haloalkyl, hydroxy, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxyalkoxy, hydroxyalkyl, aminoalkyl, aminocarbonyl, alkyl(alkoxycarbonylalkyl) aminoalkyl, heterocyclyl, heterocyclylalkyl, carboxaldehyde, carboxaldehyde hydrazone, carboxamide, alkoxycarbonylalkyl, carboxy, carboxyalkyl, carboxyalkyl, carboxyalkoxy, carboxythioalkoxy, carboxycycloalkoxy, thioalkoxy, carboxyalkylamino, trans-cinnamyl, hydroxyalkylaminocarbonyl, cyano, amino, heterocyclylalkylamino, and heterocyclylalkylaminocarbonyl; and

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, $R^{12}$and R^{13} are unsubstituted or substituted with at least one electron donating or electron withdrawing group;

or a pharmaceutically-acceptable salt, optical isomer or prodrug thereof.

Presently preferred compounds of Formula I have R^3 as Formula II (shown above), with substituents defined as above, R^1 and R^2 each independently as hydrogen, halogen, haloalkyl or nitro; and R^4 and R^5 each independently as hydrogen or alkyl.

The present invention is also directed to compounds of the structure



Formula III

wherein R^1, R^2, R^4 and R^5 are each independently selected from the group consisting of hydrogen, halogen, alkyl, haloalkyl, alkoxy, cyano, nitro, cycloalkyl and carboxaldehyde;

D, B, Y and Z are as defined above;

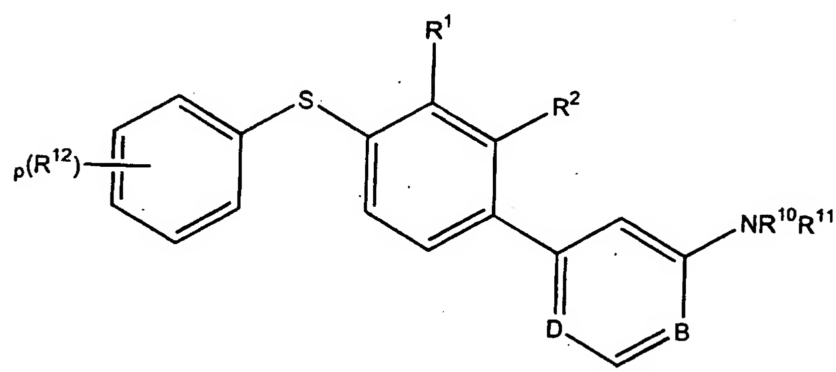
R^{12}, at each occurrence, is independently selected from the group consisting of hydrogen, halogen, alkyl, haloalkyl, alkoxy, carboxyalkoxy, carboxyalkyl and heterocyclyl; and,

p is an integer of zero to five;

wherein R^1, R^2, R^4, R^5, R^{10}, R^{11} and R^{12} are unsubstituted or substituted with at least one electron donating group or electron withdrawing group.

Presently most preferred compounds of Formula III have p as one; R^4 and R^5 as hydrogen; R^{12} as halogen, alkyl, alkoxy, carboxyalkoxy, carboxyalkyl or heterocyclyl; and R^{10} and R^{11} joined to form a three to seven membered heterocyclyl ring; said ring being piperidine, piperazine, morpholine, pyrrolidine or azetidine.

Presently most preferred compounds are of the structure



Formula IV

wherein D and B are each independently selected from the group consisting of $-N=$ and $-CR^6=$;

R^1 and R^2 are each independently selected from the group consisting of hydrogen, halogen and haloalkyl;

R^{10} and R^{11} are as defined above for Formula I;

R^{12}, at each occurrence, is independently selected from the group consisting of hydrogen, halogen, alkyl, haloalkyl, alkoxy, carboxyalkoxy, carboxyalkyl and heterocyclyl; and,

p is an integer of zero to five;

wherein R^1, R^2, R^{10}, R^{11} and R^{12} are unsubstituted or substituted with at least one electron donating group or electron withdrawing group.

For presently most preferred compounds of Formula IV, p may be one; R^{12} may be halogen, alkyl, alkoxy, carboxyalkoxy, carboxyalkyl or heterocyclyl; and R^{10} and R^{11} may be joined to form a three to seven membered heterocyclyl ring; said ring being piperidine, piperazine, morpholine, pyrrolidine or azetidine.

The compounds represented by structural Formula I, above, may be prepared by synthetic processes or by metabolic processes. Processes for the preparation of the compounds of the present invention by metabolic processes include those occurring in the human or animal body (*in vivo*) or by processes occurring *in vitro.*

The present invention is also directed to a method of treatment or prophylaxis in which the inhibition of inflammation or suppression of immune response is desired, comprising administering an effective amount of a compound having Formula I.

In yet another embodiment of the invention are disclosed pharmaceutical compositions containing compounds of Formula I.

Detailed Description of the Invention

Definition of Terms

The term "alkanoyl" as used herein refers to an alkyl group attached to the parent molecular group through a carbonyl group.

The term "alkanoylamino" as used herein refers to an alkanoyl group attached to the parent molecular group though an amino group.

The term "alkanoylaminoalkyl" as used herein refers to an alkanoylamino group attached to the parent molecular group through an alkyl group.

The term "alkanoyloxy" as used herein refers to an alkanoyl group attached to the parent molecular group through an oxygen radical.

The term "alkanoyloxyalkyl" as used herein refers to an alkanoyloxy group attached to the parent molecular group through an alkyl group.

The term "alkoxy" as used herein refers to an alkyl group attached to the parent molecular group through an oxygen atom.

The term "alkoxyalkoxy" as used herein refers to an alkoxy group attached to the parent molecular group through an alkoxy group.

The term "alkoxyalkyl" as used herein refers to an alkoxy group attached to the parent molecular group through an alkyl group.

The term "alkoxycarbonyl" as used herein refers to an alkoxy group attached to the parent molecular group through a carbonyl group.

The term “alkoxycarbonylalkyl” as used herein refers to an alkoxycarbonyl group attached to the parent molecular group through an alkyl group.

The term "alkyl" as used herein refers to a saturated straight or branched chain group of 1-10 carbon atoms derived from an alkane by the removal of one hydrogen atom.

The term “alkyl(alkoxycarbonylalkyl)amino” as used herein refers to an amino group substituted with one alkyl group and one alkoxycarbonylalkyl group.

The term “alkyl(alkoxycarbonylalkyl)aminoalkyl” as used herein refers to an alkyl(alkoxycarbonylalkyl)amino group attached to the parent molecular group through an alkyl group.

The term "alkylene" as used herein refers to a divalent group of 1-10 carbon atoms derived from a straight or branched chain alkane by the removal of two hydrogen atoms.

The term "alkylsulfonyl" as used herein refers to an alkyl radical attached to the parent molecular group through an $-SO_2-$ group.

The term “alkylsulfonylaminocarbonyl” as used herein refers to an alkylsulfonyl group attached to the parent molecular group through an aminocarbonyl group.

The term "amino" as used herein refers to a radical of the form $-NR_aR_b$, or to a radical of the form $-NR_a-$, where R_a and R_b are independently selected from hydrogen, alkyl or cycloalkyl.

The term “aminoalkanoyl” as used herein refers to an amino group attached to the parent molecular group through an alkanoyl group.

The term “aminoalkyl” as used herein refers to an amino group attached to the parent molecular group through an alkyl group.

The term "aminocarbonyl" as used herein refers to an amino group attached to the parent molecular group through a carbonyl group.

The term "aryl" as used herein refers to a mono- or bicyclic carbocyclic ring system having one or two aromatic rings. The aryl group can also be fused to a cyclohexane, cyclohexene, cyclopentane or cyclopentene ring. The aryl groups of this invention can be optionally substituted with alkyl, halogen, hydroxy, or alkoxy substituents.

The term "arylalkoxy" as used herein refers to an aryl group attached to the parent molecular group through an alkoxy group.

The term "arylalkoxycarbonyl" as used herein refers to an arylalkoxy group attached to the parent molecular group through a carbonyl group.

The term "arylsulfonyl" as used herein refers to an aryl radical attached to the parent molecular group through an $-SO_2-$ group.

The term "arylsulfonylaminocarbonyl" as used herein refers to an arylsulfonyl group attached to the parent molecular group through an aminocarbonyl group.

The term "carboxaldehyde" as used herein refers to the radical -CHO.

The term "carboxaldehyde hydrazone" as used herein refers to the radical $-CH=N-NR_cR_d$, where R_c and R_d are independently selected from hydrogen, alkyl or cycloalkyl.

The terms "carboxamide" or "carboxamido" as used herein refer to an amino group attached to the parent molecular group through a carbonyl group.

The term "carboxamidoalkyl" as used herein refers to a carboxamido group attached to the parent molecular group through an alkyl group.

The term “carboxy” as used herein refers to the radical -COOH.

The term “carboxyalkyl” as used herein refers to a carboxy group attached to the parent molecular group through an alkyl group.

The term “carboxyalkylamino” as used herein refers to a carboxyalkyl group attached to the parent molecular group through an amino group.

The term “carboxyalkoxy” as used herein refers to a carboxy group attached to the parent molecular group through an alkoxy group.

The term “carboxycarbonyl” as used herein refers to a carboxy group attached to the parent molecular group through a carbonyl group.

The term “carboxycycloalkoxy” as used herein refers to a carboxy group attached to the parent molecular group through a cycloalkoxy group.

The term “carboxythioalkoxy” as used herein refers to a carboxy group attached to the parent molecular group through a thioalkoxy group.

The term “cyano” as used herein refers to the radical -CN.

The term "cycloalkyl" as used herein refers to a monovalent saturated cyclic or bicyclic hydrocarbon group of 3-12 carbons derived from a cycloalkane by the removal of a single hydrogen atom. Cycloalkyl groups may be optionally substituted with alkyl, alkoxy, halo, or hydroxy substituents.

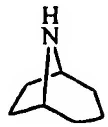
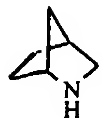
The term “cycloalkoxy” as used herein refers to a monovalent saturated cyclic or bicyclic hydrocarbon group of 3-12 carbons derived from a cycloalkane by the removal of a single hydrogen atom, linked to the parent molecular group through an oxygen atom. Cycloalkoxy groups may be optionally substituted with alkyl, alkoxy, halo or hydroxy groups.

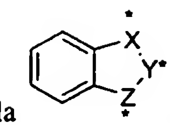
The terms "halo" or "halogen" as used herein refers to F, Cl, Br, or I.

The term "haloalkyl" as used herein refers to an alkyl group substituted with one or more halogen atoms.

The terms "heterocycle" or "heterocyclyl" represent a 4-, 5-, 6- or 7-membered ring containing one, two or three heteroatoms independently selected from the group consisting of nitrogen, oxygen and sulfur. The 4- and 5-membered rings have zero to two double bonds and the 6- and 7-membered rings have zero to three double bonds. The term "heterocycle" or "heterocyclic" as used herein additionally refers to bicyclic, tricyclic and tetracyclic groups in which any of the above heterocyclic rings is fused to one or two rings independently selected from an aryl ring, a cyclohexane ring, a cyclohexene ring, a cyclopentane ring, a cyclopentene ring or another monocyclic heterocyclic ring. Heterocycles include acridinyl, benzimidazolyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, biotinyl, cinnolinyl, dihydrofuryl, dihydroindolyl, dihydropyranyl, dihydrothienyl, dithiazolyl, furyl, homopiperidinyl, imidazolidinyl, imidazolinyl, imidazolyl, indolyl, isoquinolyl, isothiazolidinyl, isothiazolyl, isoxazolidinyl, isoxazolyl, morpholinyl, oxadiazolyl, oxazolidinyl, oxazolyl, piperazinyl, piperidinyl, pyranyl, pyrazolidinyl, pyrazinyl, pyrazolyl, pyrazolinyl, pyridazinyl, pyridyl, pyrimidinyl, pyrimidyl, pyrrolidinyl, pyrrolidin-2-onyl, pyrrolinyl, pyrrolyl, quinolinyl, quinoxaloyl, tetrahydrofuryl, tetrahydroisoquinolyl, tetrahydroquinolyl, tetrazolyl, thiadiazolyl, thiazolidinyl, thiazolyl, thienyl, thiomorpholinyl, triazolyl, and the like.

Heterocyclics also include bridged bicyclic groups where a monocyclic heterocyclic group is bridged by an alkylene group such as

, , , and the like.

Heterocyclics also include compounds of the formula  where X* and Z* are independently selected from $-CH_2-$, $-CH_2NH-$, $-CH_2O-$, -NH- and -O-, with the proviso that at least one of X* and Z* is not $-CH_2-$, and Y* is selected from -C(O)- and $-(C(R'')_2)_v-$, where R" is hydrogen or alkyl of one to four carbons, and v is 1-3. These heterocycles include 1,3-benzodioxolyl, 1,4-benzodioxanyl, 1,3-benzimidazol-2-one and the like. The heterocycle groups of this invention can be optionally substituted with alkyl, halogen, hydroxy or alkoxy substituents.

The term "heterocyclylalkyl" as used herein refers to a heterocyclic group attached to the parent molecular group through an alkyl group.

The term "heterocyclylalkylamino" as used herein refers to an heterocyclylalkyl group attached to the parent molecular group through an amino group.

The term "heterocyclylalkylaminocarbonyl" as used herein refers to a heterocyclylalkylamino group attached to the parent molecular group through a carbonyl group.

The term "heterocyclylamino" as used herein refers to a heterocyclyl group attached to the parent molecular group through an amino group.

The term "heterocyclylcarbonyl" as used herein refers to a heterocyclyl group attached to the parent molecular group through a carbonyl group.

The term "heterocyclylsulfonyl" as used herein refers to a heterocyclyl radical attached to the parent molecular group through an $-SO_2-$ group.

The term "heterocyclylsulfonylaminocarbonyl" as used herein refers to a heterocyclylsulfonyl group attached to the parent molecular group through an aminocarbonyl group.

The term "hydroxyalkanoyl" as used herein refers to a hydroxy radical attached to the parent molecular group through an alkanoyl group.

The term "hydroxyalkoxy" as used herein refers to a hydroxy radical attached to the parent molecular group through an alkoxy group.

The term "hydroxyalkoxyalkyl" as used herein refers to a hydroxyalkoxy group attached to the parent molecular group through an alkyl group.

The term "hydroxyalkyl" as used herein refers to a hydroxy radical attached to the parent molecular group through an alkyl group.

The term "hydroxyalkylaminocarbonyl" as used herein refers to a hydroxyalkyl group attached to the parent molecular group through an aminocarbonyl group.

The term "perfluoroalkyl" as used herein refers to an alkyl group in which all of the hydrogen atoms have been replaced by fluoride atoms.

The term "phenyl" as used herein refers to a monocyclic carbocyclic ring system having one aromatic ring. The phenyl group can also be fused to a cyclohexane or cyclopentane ring. The phenyl groups of this invention can be optionally substituted with alkyl, halogen, hydroxy or alkoxy substituents.

The term "pharmaceutically-acceptable prodrugs" as used herein represents those prodrugs of the compounds of the present invention which are, within the scope of sound

medical judgment, suitable for use in contact with the tissues of humans and lower animals with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention.

The term "prodrug," as used herein, represents compounds which are rapidly transformed *in vivo* to the parent compound of the above formula, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference. The term "sulfonate" as used herein refers to the radical $-SO_3H$.

The term "tetrazole" or "tetrazolyl" as used herein refers to the heterocyclic radical $-CN_4H$.

The term "thioalkoxy" as used herein refers to an alkyl group attached to the parent molecular group through a sulfur atom.

The term "trans-cinnamyl" as used herein refers to an acrylamido group (aminocarbonylethenyl) attached to the parent molecular group through C-3 of the acrylamido group, such that the aminocarbonyl and the parent molecular group exist in a trans relationship about the ethenyl group.

The term "lower" refers to a C_1-C_6 unit for a particular functionality. For example, "lower alkyl" means C_1-C_6 alkyl.

Use of the above terms is meant to encompass substituted and unsubstituted moieties. Substitution may be by one or more groups such as alcohols, ethers, esters,

amides, sulfones, sulfides, hydroxyl, nitro, cyano, carboxy, amines, heteroatoms, lower alkyl, lower alkoxy, lower alkoxycarbonyl, alkoxyalkoxy, acyloxy, halogen, trifluoromethoxy, trifluoromethyl, aralkyl, alkenyl, alkynyl, aryl, carboxyalkoxy, carboxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, alkylheterocyclyl, heterocyclylalkyl, oxo, arylsulfonaminocarbonyl or any of the substituents of the preceding paragraphs or any of those substituents either attached directly or by suitable linkers. The linkers are typically short chains of 1-3 atoms containing any combination of –C-, -C(O)-, -NH-, -S-, -S(O)-, -O-, -C(O)O- or –S(O)-. Rings may be substituted multiple times.

The terms "electron-withdrawing" or "electron-donating" refer to the ability of a substituent to withdraw or donate electrons relative to that of hydrogen if hydrogen occupied the same position in the molecule. These terms are well-understood by one skilled in the art and are discussed in Advanced Organic Chemistry by J. March, 1985, pp. 16-18, incorporated herein by reference.

Electron withdrawing groups include halo, nitro, carboxyl, lower alkenyl, lower alkynyl, carboxaldehyde, carboxyamido, aryl, quaternary ammonium and trifluoromethyl among others. Electron donating groups include such groups as hydroxy, lower alkyl, amino, lower alkylamino, di(lower alkyl)amino, aryloxy, mercapto, lower alkylthio, lower alkylmercapto and disulfide among others. One skilled in the art will appreciate that the aforesaid substituents may have electron donating or electron withdrawing properties under different chemical conditions. Moreover, the present invention contemplates any combination of substituents selected from the above-identified groups.

The most preferred electron donating or electron withdrawing substituents are halo, nitro, alkanoyl, carboxaldehyde, arylalkanoyl, aryloxy, carboxyl, carboxamide, cyano, sulfonyl, sulfoxide, heterocyclyl, guanidine, quaternary ammonium, lower alkenyl, lower alkynyl, sulfonium salts, hydroxy, lower alkoxy, lower alkyl, amino, lower alkylamino, di(lower alkylamino), amine lower mercapto, mercaptoalkyl, alkylthio and alkyldithio.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from a combination of the specified ingredients in the specified amounts.

Compounds of the present invention can exist as stereoisomers wherein asymmetric or chiral centers are present. These compounds are designated by the symbols "R" or "S," depending on the configuration of substituents around the chiral carbon atom. The present invention contemplates various stereoisomers and mixtures thereof. Stereoisomers include enantiomers and diastereomers, and mixtures of enantiomers or diastereomers are designated ($\pm$). Individual stereoisomers of compounds of the present invention can be prepared synthetically from commercially available starting materials which contain asymmetric or chiral centers or by preparation of racemic mixtures followed by resolution well-known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the

auxiliary, (2) salt formation employing an optically active resolving agent, or (3) direct separation of the mixture of optical enantiomers on chiral chromatographic columns.

Geometric isomers can also exist in the compounds of the present invention. The present invention contemplates the various geometric isomers and mixtures thereof resulting from the arrangement of substituents around a carbon-carbon double bond or arrangement of substituents around a carbocyclic ring. Substituents around a carbon-carbon double bond are designated as being in the Z or E configuration wherein the term "Z" represents substituents on the same side of the carbon-carbon double bond and the term "E" represents substituents on opposite sides of the carbon-carbon double bond. The arrangement of substituents around a carbocyclic ring are designated as cis or trans wherein the term "cis" represents substituents on the same side of the plane of the ring and the term "trans" represents substituents on opposite sides of the plane of the ring. Mixtures of compounds wherein the substituents are disposed on both the same and opposite sides of plane of the ring are designated cis/trans.

As is apparent from the foregoing descriptions, the compounds of Formula I are useful in a variety of forms, i.e., with various substitutions as identified. Examples of particularly desirable compounds are quite diverse, and many are mentioned herein.

Compounds of the present invention include, but are not limited to: 1-(6-(4-(2-isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-yl)-piperidine-3-carboxylic acid, 4-(4-(2-isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-6-(3-(2*H*-tetrazol-5-yl)-piperidin-1-yl)-pyrimidine, 4-(4-(2-isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-6-(4-(2*H*-tetrazol-5-yl)-piperidin-1-yl)-pyrimidine, (1-(6-(4-(2-isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-yl)-piperidin-3-yl)-

methanol, 2-(1-(6-(4-(2-isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-yl)-piperidin-4-yl)-ethanol, *N*-(1-(4-(4-(2-isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-pyrrolidin-3-yl)-acetamide, 1-(4-(4-(2-methoxy-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-pyrrolidine-3-ol, *N*-1-(4-(4-(2-methoxy-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-pyrrolidine-3-yl)-acetamide, *N*-1-(4-(4-(2-methoxy-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-pyrrolidine-3-yl)-acetamide, *N*-(1-(4-(4-(2,3-dihydro-benzo(1,4)dioxin-6-ylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-pyrrolidin-3-yl)-acetamide, 4'-(4-(2,3-dihydro-benzo(1,4)dioxin-6-ylsulfanyl)-3-trifluoromethyl-phenyl)-3,4,5,6-tetrahydro-2*H*-(1,2')bipyridinyl-4-carboxylic acid and 4'-(4-(2,3-dihydro-benzo(1,4)dioxin-6-ylsulfanyl)-3-trifluoromethyl-phenyl)- 3,4,5,6-tetrahydro-2*H*-(1,2')bipyridinyl-3-carboxylic acid.

Abbreviations

Abbreviations which have been used in the schemes and the examples which follow are: DCM for methylene dichloride; EWG for electron withdrawing group; NMP for N-methylpyrrolidinone; sat. for saturated; THF for tetrahydrofuran; TFA for trifluoroacetic acid; ; BINAP for 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl; DMSO for dimethylsulfoxide; MCPBA for meta-chloroperbenzoic acid; DMF for dimethylformamide; TLC for thin layer chromatography; HPLC for high pressure liquid chromatography; APCI for atmospheric pressure chemical ionization; ESI for electrospray ionization; DCI for direct chemical ionization; LFA for lymphocyte function-associated antigen; and ICAM for intercellular adhesion molecule.

Pharmaceutical Compositions and Methods of Treatment

The present invention also provides pharmaceutical compositions which comprise compounds of the present invention formulated together with one or more pharmaceutically-acceptable carriers. The pharmaceutical compositions may be specially formulated for oral administration in solid or liquid form, for parenteral injection, or for rectal administration.

The pharmaceutical compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), bucally, or as an oral or nasal spray. The term "parenteral" administration as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Pharmaceutical compositions of this invention for parenteral injection comprise pharmaceutically-acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservative, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents such as sugars, sodium chloride, and the like, Prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of the drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid

compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically-acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or (a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, (c) humectants such as glycerol, (d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, (e) solution retarding agents such as paraffin, (f) absorption accelerators such as quaternary ammonium compounds, (g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, (h) absorbents such as kaolin and bentonite clay, and (I) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or

preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically-acceptable emulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethyl formamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, and tragacanth, and mixtures thereof.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-

irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at room temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically-acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and the phosphatidyl cholines (lecithins), both natural and synthetic.

Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 et seq.

The compounds of the present invention may be used in the form of pharmaceutically-acceptable salts derived from inorganic or organic acids. By "pharmaceutically-acceptable salt" is meant those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically-acceptable salts are well-known in the art. For example, S. M. Berge, *et al.* describe pharmaceutically-acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66: 1 *et seq*. The salts may

be prepared *in situ* during the final isolation and purification of the compounds of the invention or separately by reacting a free base function with a suitable acid. Representative acid addition salts include, but are not limited to acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate (isethionate), lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, phosphate, glutamate, bicarbonate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; arylalkyl halides like benzyl and phenethyl bromides and others. Water or oil-soluble or dispersible products are thereby obtained. Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, hydrobromic acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid.

Basic addition salts can be prepared *in situ* during the final isolation and purification of compounds of this invention by reacting a carboxylic acid-containing moiety with a suitable base such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia or an organic primary, secondary or tertiary amine. Pharmaceutically-acceptable basic addition salts include, but

are not limited to, cations based on alkali metals or alkaline earth metals such as lithium, sodium, potassium, calcium, magnesium and aluminum salts and the like and nontoxic quaternary ammonia and amine cations including ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine and the like. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, piperazine and the like.

Dosage forms for topical administration of a compound of this invention include powders, sprays, ointments and inhalants. The active compound is mixed under sterile conditions with a pharmaceutically-acceptable carrier and any needed preservatives, buffers, or propellants which may be required. Opthalmic formulations, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

Actual dosage levels of active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active compound(s) that is effective to achieve the desired therapeutic response for a particular patient, compositions, and mode of administration. The selected dosage level will depend upon the activity of the particular compound, the route of administration, the severity of the condition being treated, and the condition and prior medical history of the patient being treated. However, it is within the skill of the art to start doses of the compound at levels lower than required for to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.

Generally dosage levels of about 0.1 to about 50 mg, more preferably of about 5 to about 20 mg of active compound per kilogram of body weight per day are administered

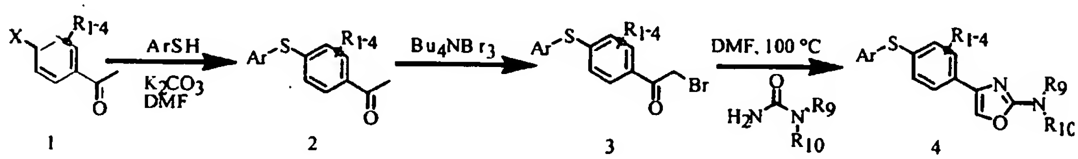
orally or intravenously to a mammalian patient. If desired, the effective daily dose may be divided into multiple doses for purposes of administration, e.g. two to four separate doses per day.

Preparation of Compounds of this Invention

The compounds and processes of the present invention may be better understood in connection with the following synthetic schemes which illustrate the methods by which the compounds of the invention can be prepared.

Scheme I describes compounds of **Formula I** which contain oxazole (n=0, Y=N, B=O, D=C). Aryl methyl ketone 1 with the approprite substitution and a leaving group X reacts with an aryl thiol to give biaryl sulfide **2**. Biarylsulfide can be converted into alpha-bromomethyl ketone **3** using a variety of reagents including Bu_4NBr_3. Condensation of **3** with a urea then gives the desired compounds **4**.

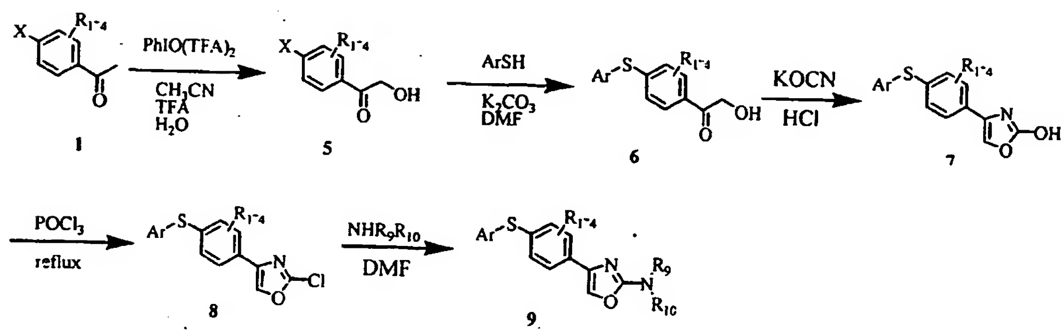
Scheme 1



Another method of preparing compounds of **Formula I** containing oxazole (n=0, Y=N, B=O, D=C) is illustrated in Scheme 2. Aryl methyl ketones 1 are converted into alpha-hydroxymethyl ketone **5**, which then can be reacted with arylthiols to give biaryl sulfide **6**. Acid-catalyzed condensation of **6** with KOCN affords 2-hydroxy oxazole **7**,

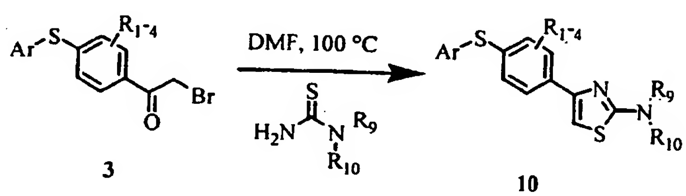
which can be converted into 2-chloro-oxazole **8** using $POCl_3$. Displacement of the chloride of **8** with amines gives the desired 2-amino-oxazole **9**.

Scheme 2



Scheme 3 describes the synthesis of a class of compounds of Formula I containing thioazole ring (n=0, Y=N, B=S, D=C). The biaryl sulfide alpha-bromomethyl ketone **3** can be prepared following the procedure outline in Scheme 1. Condensation of **3** with a properly substituted thiourea gives the desired 2-aminothioazole **10**.

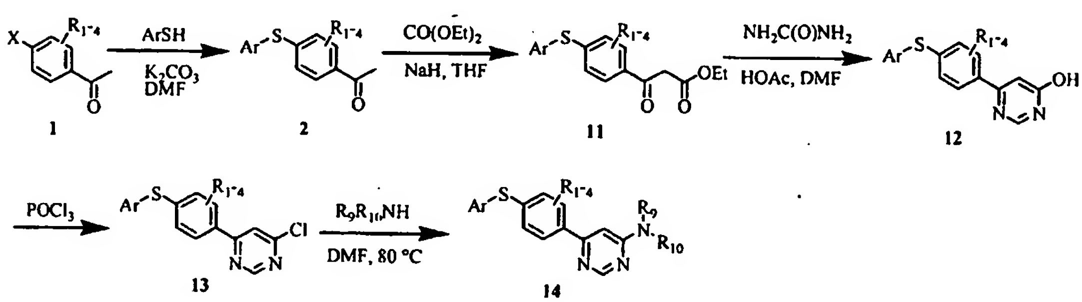
Scheme 3



Another class of compounds of Formula I are compounds containing pyrimidine ring, for example 4,6-disubstituted pyrimidines (n=1, Y=C, B=N, Z=C, D=N). Scheme 4

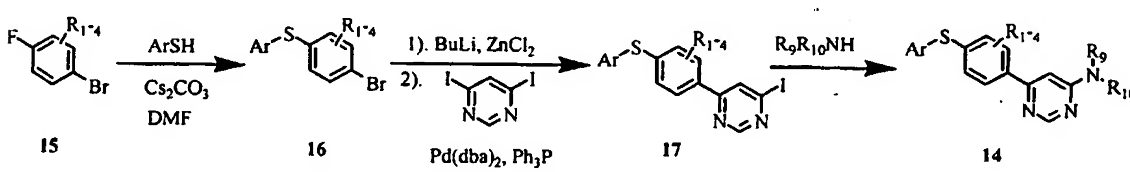
describes one procedure for the preparation of this class of compounds. Reaction of biaryl sulfide methyl ketone **2** with diethyl carbonate under base-catalysis leads to beta-ketoester **11**. Condensation of **11** with formamidine gives 4-hydroxy pyrimidine **12**, which can be converted into 4-chloropyrimidine **13**. Displacement of the chloride of **13** by amines then gives the desired 4-amino-pyrimidine **14**.

Scheme 4



An alternative synthesis of the 4,6-disubstituted pyrimidines is illustrated in Scheme 5. Nucleophilic substitution of aryl fluoride **15** with aryl thiol under base-catalysis gives biaryl sulfide **16**. Transmetallation of **16** with n-BuLi/$ZnCl_2$, followed by Pd-catalyzed cross-coupling with 4,6-diiodopyrimidine leads to iodopyrimidine **17**. Reaction of **17** with selected amines gives the desired 4-aminopyrimidine **14**.

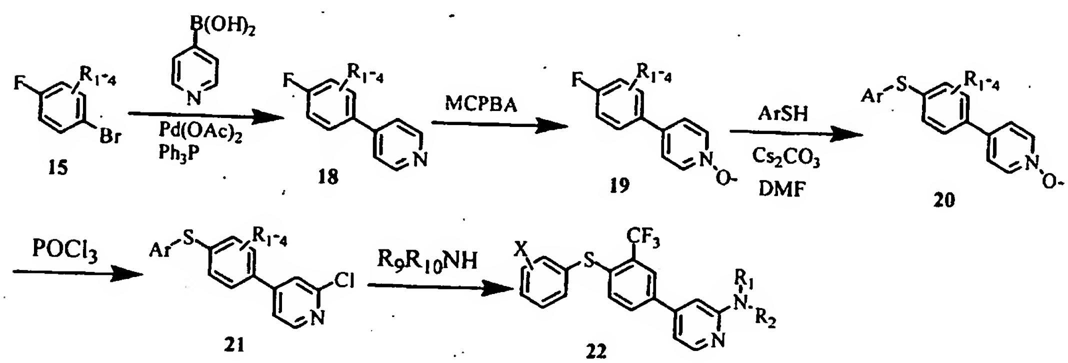
Scheme 5



Yet another class of compounds of Formula I are compounds containing a pyridine ring, for example 2,4-disubstituted pyridines (n=1, Y=C, B=N, Z=C, D=C). Scheme 6 describes one procedure for the preparation of this class of compounds. Thus,

Pd-catalyzed cross-coupling of properly substituted 1-bromo-4-fluoro-benzene **15** and 4-pyridine boronic acid gives compounds **18**. Oxidation of **18** with MCPBA leads to pyridinium oxide **19**. Displacement of the fluoride of **19** with aryl thiols then affords biarylsulfide **20**. Treatment of **20** with $POCl_3$ leads to 2-chloropyridine **21**. Finally, reaction of **21** with selected amines gives the desired 2-aminopyridines **22**.

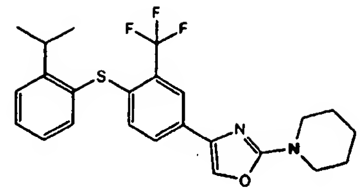
Scheme 6



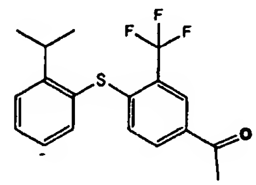
The compounds and processes of the present invention will be better understood in connection with the following examples which are intended as an illustration of and not a limitation upon the scope of the invention.

Example 1

1-{4-[4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl]-oxazol-2-yl}-piperidine **23** was synthesized as follows.

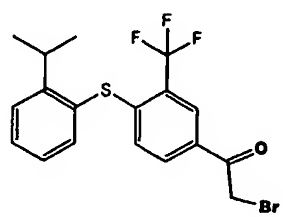


23



24

1A. First, 1-(4-isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-ethanone 24 was prepared as follows. To a solution of o-isopropyl thiophenol (2.46 ml, 15 mmole) and 4-fluoro-3-trifluoromethyl acetophenone (3.0 g, 14.6 mmole) in 100 ml of DMF was added Cs_2CO_3 (7.15 g, 22 mmole). After stirring for 3 hours, the mixture was filtered and solvent was removed by evaporation. The residue was chromatographed on a silica gel column, eluting with 5% EtOAc in hexane, giving 4.70 g of a white solid **24**. Yield: 96.6%. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ1.18 (d, J =6.6 Hz, 6H), 2.56 (s, 3H), 3.45 (heptet, J = 6.6 Hz, 1H), 6.81 (d, J=8.4 Hz, 1H), 7.26 (m, 1H), 4.48 (d, J=1.8 Hz, 1H), 7.50 (d, J=1.8 Hz, 1H), 7.53 (d, J=8.1 Hz, 1H), 7.79 (d, J = 8.1 Hz, 1H), 8.21 (d, J = 1.8 Hz, 1H); MS (DCI/NH_3) m/z 339 $(M+H)^+$; 356 $(M+NH^4)^+$.



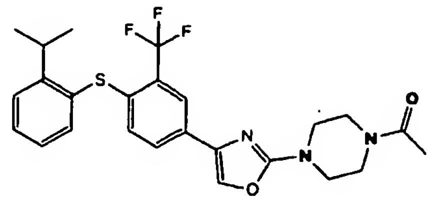
25

1B. Then 2-bromo-1-(4-isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-ethanone **25** was prepared as follows. Compound **24** (4.72 g, 14.0 mmole) and tetrabutylammonium tribromide (7.6 g, 15.4 mmole) was dissolved in a mixture of 20 ml of MeOH and 50 ml of DCM. The solution was stirred at ambient temperature overnight. The solvent was then evaporated and the residue was chromatographed on a silica gel column, eluting with 10% EtOAc in hexane. An off-white solid **25** was obtained, 5.9 g, 100%. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ1.18 (d, J =6.9 Hz, 6H), 3.45 (heptate, J = 6.9 Hz, 1H), 4.35 (s, 2H), 6.81 (d, J=8.4 Hz, 1H), 7.29 (d.d, J=2.4, 6.3 Hz, 1H), 7.48 (d, J=1.8 Hz, 1H), 7.48-7.56 (m, 3H), 7.81 (d.d, J=2.4, 6.3 Hz, 1H), 7.79 (d, J = 8.1 Hz, 1H), 8.24 (d, J = 1.8 Hz, 1H); MS (DCI/NH_3) m/z 418 $(M+H)^+$; 434 $(M+NH^4)^+$.

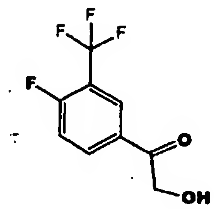
1C. A solution of compound **25** (22 mg, 0.05 mmole) and 1-carbamyl piperidine (32 mg, 0.25 mmole) was stirred at 105 °C for 2 hours. DMF was then evaporated and the residue purified on a preparative HPLC system with a C_8 reverse-phase column using 10 mM H_4NOAc (aq.) and CH_3CN as the mobile phase. The product **23** was obtained as a yellow solid (16 mg) from the HPLC fractions by evaporating the solvents on a speedvac. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ1.18 (d, J =6.9 Hz, 6H), 1.5-1.7 (m, 6H), 3.5-3.7 (m, 5 H), 6.91 (d, J=8.4 Hz, 1H), 7.34-7.38 (m, 3H), 7.47 (s, 1H), 7.58-7.60 (m, 1H), 7.96 (s, 1H). MS (APCI) m/z 447 $(M+H)^+$.

Example 2

1-(4-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-oxazol-2-yl)piperidine **26** was synthesized according to the following procedure.

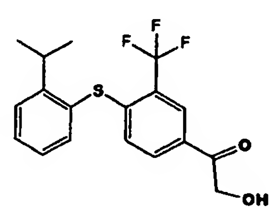


26

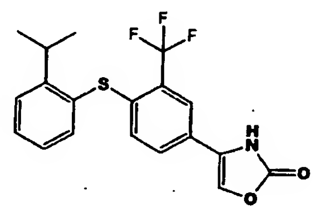


27

2A. First, 1-(4-fluoro-3-trifluoromethyl-phenyl)-2-hydroxy-ethanone **27** was prepared as follows. To a solution of 1-fluoro-3-trifluoroacetophenone (1.0 g, 5.0 mmole) in acetonitrile (15 ml) and water (3 ml) was added trifluoroacetic acid (0.77 ml, 10 mmole) and bis-(trifluoroacetoxyl)iodobenzene (4.3 g, 10 mmole). The mixture was refluxed for three hours. The solution was concentrated and then extracted with EtOAc (3 x 30 ml). The combined organic solution was washed with 5% aq. $NaHCO_3$ and dried. After filtration and solvent evaporation, the residue was chromatographed on a silica gel column, eluting with 30% EtOAc in hexane, giving 0.47 g of a white solid **27**, 37.8 % yield. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.28 (br s, 1 H), 4.89 (s, 2H), 7.36 (t, J=9 Hz, 1H), 8.12-8.17 (m, 1H), 8.21 (d, J=6 Hz, 3H); MS (APCI) m/z 223 $(M+H)^+$.



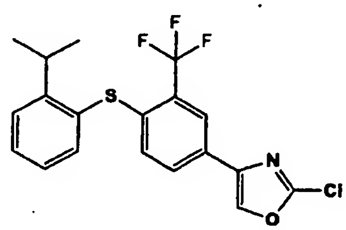
2B. Then 2-hydroxy-1-(4-(2-isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-ethanone **28** was prepared as follows. To a solution of compound **27** (0.4 g, 1.8 mmole) and o-isopropylthiophenol (0.31 ml, 1.8 mmole) in DMF (10 ml) was added Cs_2CO_3 (0.59 g, 1.8 mmole). The mixture was stirred for 10 minutes and EtOAc (30 ml) was added. The mixture was filtered, concentrated and chromatographed on a silica gel column eluting with 30% EtOAc in hexane. The desired product **28** was obtained as an oil, 0.22 g, 34.8%. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ1.17 (d, J= 7.0 Hz, 6 H), 3.40-3.46 (m, 2 H), 4.80 (s, 2H), 6.82 (d, J=8.4 Hz, 1H), 7.27-7.31 (m, 1H), 7.51-7.55 (m, 3H), 7.72 (d, J=8.4 Hz, 1H), 8.17 (s, 1H); MS (DCI/NH_3) m/z 355 $(M+H)^+$, 372 $(M+NH_4)^+$.



29

2C. Then 4-(4-(2-isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-3H-oxaxol-2-one **29** was prepared as follows. To a solution of compound **28** (0.22 g, 0.62 mmole) and potassium cyanate 0.25 g, 3.0 mmole) in DMF 5.0 ml) was added 0.5 ml of 4 M HCl in dioxane. The mixture was stirred at ambient temperature for 3 hours and another 0.25 ml of 4 M HCl in dioxane was added. The mixture was stirred for another 10 minutes and then quenched with water (20 ml). The layers were separated and the organic layer was extracted with EtOAc. The combined organic solution was dried, filtered and concentrated. Chromatography of the residue gave the title compound **29** as a yellow solid. 194 mg, 82.6%. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ1.18 (d, J= 7.0 Hz, 6H),

3.48 (heptet, J=7.0 Hz, 1H), 6.87 (d, J=8.1 Hz, 1H), 7.11 (s, 1H), 7.27 (m, 2H), 7.44-7.48 (m, 3H), 7.64 (s, 1H), 9.75 (s, 1H); MS (DCI/NH_3) m/z 397 $(M+NH_4)^+$.



30

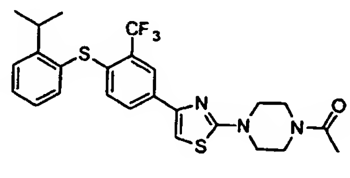
2D. Then, 2-chloro-4-(4-(2-isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-oxazole **30** was prepared as follows. A solution of compound **29** (197 mg, 0.52 mmole) and diethylphenylamine (0.085 ml) in phosphorus oxychloride (5.0 ml) was refluxed for two hours. The mixture was then concentrated and the residue was quenched with ice-water, followed by extraction with EtOAc. The EtOAc solution was dried, filtered and concentrated. The residue was chromatographed on a 10-g silica gel cartridge, eluting with 30% EtOAc in hexane. The title compound **30** was obtained as a yellow solid. 97 mg, 47.0% yield. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ1.19 (d, J=7.0 Hz, 6H), 3.50 (heptet, J=7.0 Hz, 1H), 6.88 (d, J=8.1 Hz, 1H), 7.20-7.23 (m, 1H), 7.42-7.44 (m, 3H), 7.55 (d, J=8.1 Hz, 1H), 7.90 (s, 1H), 7.97 (s, 1H); MS (DCI/NH_3) m/z 398 (M+H), 415 $(M+NH_4)^+$.

2E. A solution of compound **30** (20 mg, 0.05 mmole) and 1-acetyl piperazine (19.2 mg, 0.15 mmole) in toluene (1.0 ml) was stirred at 100 °C for five hours. Solvent was evaporated and the residue was purified on a 5-g silica gel cartridge eluting with EtOAc. The title compound **26** was obtained as a white solid. 11.2 mg, 45.8%. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ1.18 (d, J=7.0 Hz, 6H), 2.15(s, 3H), 3.49-3.62 (m, 7H), 3.74

(m, 2H), 6.89 (d, J=8.0 Hz, 1H), 7.15-7.21 (m, 2H), 7.39-7.41 (m, 2H), 7.52 (s, 1H), 7.58 (d, J=8.0 Hz, 1H), 7.96 (s, 1H); MS (APCI) m/z 490$(M+H)^+$.

Example 3

1-(4-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-thiazol-2-yl)-piperazin-1-yl)-ethanone **31** was synthesized according to the following procedure.

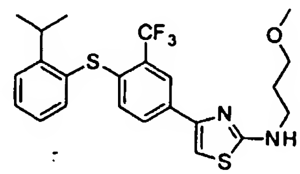


31

A solution of compound **25** (40 mg, 1.0 mmole) and 1-acetyl-4-thiocarbamyl piperazine (19 mg, 0.1 mmole) in 1.0 ml of DMF was stirred at ambient temperature for 16 hours. Then the solvent was evaporated and the residue was purified on a preparative HPLC with a C_8 reverse phase column, eluting with a gradient of acetonitrile and 10 mM NH_4OAc buffer. The title compound **31** was obtained as a yellow solid. 45 mg, 80.0% yield. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ1.12 (d, J= 6.0 Hz, 6H), 2.08 (s, 3H), 3.40-3.49 (m, 3H), 3.55 (br s, 2H), 3.71 (m, 2H), 6.74 (s, 1H), 6.83 (d, J=6.0 Hz, 1H), 7.08-7.13 (m, 1H), 7.31-7.34 (m, 3H), 7.64 (d, J=6.0 Hz, 1H), 8.05 (s, 1H); MS (DCI/NH_3) m/z 490 $(M+H)^+$.

Example 4

(4-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-thiazol-2-yl)-(3-methoxy-propyl)-amine **32** was synthesized according to the following procedure.

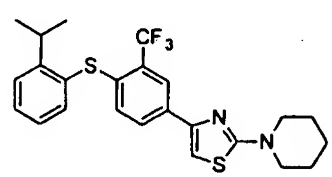


32

The title compound was prepared according to the procedure of Example 3 from compound **25** (20 mg, 0.05 mmole) and *N*-(1-methoxy)propyl thiourea (14.8 mg, 0.1 mmole). Yield: 11.7 mg, 50.8%. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ1.18 (d, J= 8.5 Hz, 6H), 1.95 (pentaplet, J=8.0 Hz, 2H), 3.36 (s, 3H), 3.42-3.45 (m, 2H), 3.51-3.54 (m, 3H), 6.66 (s, 1H), 6.90 (d, J=10.5 Hz, 1H), 7.17-7.20 (m, 1H), 7.39-7.42 (m, 3H), 7.68 (dd, J=10.5 and 2.0 Hz, 1H), 8.06 (d, J=2.0 Hz, 1H). MS (DCI/NH_3) m/z 467 $(M+H)^+$.

Example 5

1-(4-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-thiazol-2-yl)-piperidine **33** was synthesized according to the following procedure.



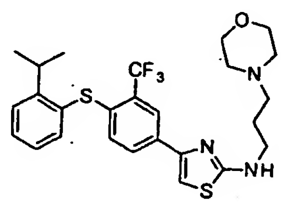
33

The title compound was prepared according to the procedure of Example 3 from compound **25** (20 mg, 0.05 mmole) and 1-thiocarbamyl-piperidine (14.4 mg, 0.1 mmole).

Yield: 4.9 mg, 10.6%. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ1.18 (d, J= 8.5 Hz, 6H), 1.95 (pentet, J=8.0 Hz, 2H), 1.56-1.72 (m, 6H), 3.50-3.57 (m, 5H), 6.70 (s, 1H), 6.91 (d, J=10.5 Hz, 1H), 7.15-7.19 (m, 1H), 7.37-7.40 (m, 3H), 7.78 (dd, J=10.5 and 2.0 Hz, 1H), 8.11 (d, J=2.0 Hz, 1H); MS (DCI/NH_3) m/z 463 $(M+H)^+$.

Example 6

(4-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-thiazol-2-yl)-(3-morpholin-4-yl-propyl)-amine **34** was synthesized according to the following procedure.

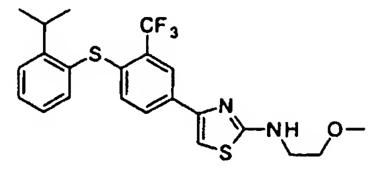


34

The title compound was prepared according to the procedure of Example 3 from compound **25** (20 mg, 0.05 mmole) and N-[1-(1'-morpholinyl)]propylthiourea (19 mg, 0.1 mmole). Yield: 25.4 mg, 97.7%. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.18 (d, J= 8.5 Hz, 6H), 1.86-1.89 (m, 2H), 2.54-2.59 (m, 6H), 3.52 (heptet, J=8.5 Hz, 1H), 3.77-3.79 (m, 4H), 6.68 (s, 1H), 6.91 (d, J=10.5 Hz, 1H), 7.15-7.19 (m, 1H), 7.38-7.40 (m, 3H), 7.69 (dd, J=10.5 and 2.0 Hz, 1H), 8.10 (d, J=2.0 Hz, 1H); MS (DCI/NH_3) m/z 522 $(M+H)^+$.

Example 7

(4-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-thiazol-2-yl)-(2-methoxy-ethyl)-amine **35** was synthesized according to the following procedure.

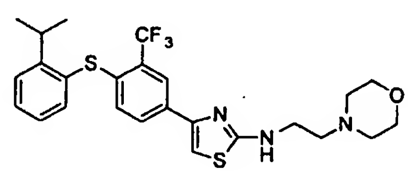


35

The title compound was prepared according to the procedure of Example 3 from compound **25** (20 mg, 0.05 mmole) and N-(1-methoxyl)ethylthiourea (14 mg, 0.1 mmole). Yield: 11 mg, 50%. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.18 (d, J= 8.5 Hz, 6H), 3.39 (s, 3H), 3.50-3.55 (m, 3H), 3.62 (t, J=5.5 Hz, 2H), 6.68 (s, 1H), 6.90 (d, J=10.5 Hz, 1H), 7.16-7.21 (m, 1H), 7.38-7.42 (m, 3H), 7.68 (dd, J=10.5 and 2.0 Hz, 1H), 8.07 (d, J=2.0 Hz, 1H); MS (DCI/NH_3) m/z 453(M+H)$^+$.

Example 8

(4-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-thiazol-2-yl)-(2-morpholin-4-yl-ethyl)-amine **36** was synthesized according to the following procedure.



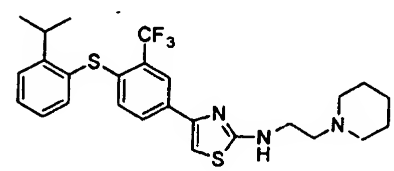
36

The title compound was prepared according to the procedure of Example 3 from compound **25** (20 mg, 0.05 mmole) and N-[1-(1'-morpholinyl)]ethyl thiourea (14 mg, 0.1 mmole). Yield: 20.3 mg, 81.2%. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.18 (d, J= 8.5 Hz, 6H), 2.56 (br s, 4H), 2.71 (br s, 2H), 3.44 (br s, 2H), 3.52 (heptet, J=8.5 Hz, 1H), 3.76-3.78 (m, 4H), 5.88 (br s, 1H), 6.70 (s, 1H), 6.91 (d, J=10.5 Hz, 1H), 7.15-7.19 (m, 1H), 7.38-7.40

(m, 3H), 7.69 (d, J=10.5 Hz, 1H), 8.12 (d, J=2.0 Hz, 1H); MS (DCI/NH_3) m/z 508 $(M+H)^+$.

Example 9

(4-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-thiazol-2-yl)-(2-piperidin-1-yl-ethyl)-amine **37** was synthesized according to the following procedure.

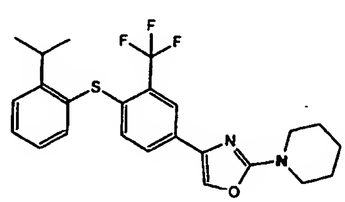


37

The title compound was prepared according to the procedure of Example 3 from compound **25** (20 mg, 0.05 mmole) and N-[1-(1'-piperidinyl)]ethyl thiourea (20 mg, 0.1 mmole). Yield: 21 mg, 85.0%. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.18 (d, J= 8.5 Hz, 6H), 1.51 (m, 2H), 1.68-1.74 (m, 4H), 2.64 (bs, 4H), 2.80 (t, J=6.5 Hz, 1H), 3.49-3.56 (m, 3H), 4.64 (bs, 1H), 6.68 (s, 1H), 6.90 (d, J=10.5 Hz, 1H), 7.15-7.19 (m, 1H), 7.38-7.41 (m, 3H), 7.69 (d, J=10.5 Hz, 1H), 8.11 (d, J=2.0 Hz, 1H). MS (DCI/NH_3) m/z 506 $(M+H)^+$.

Example 10

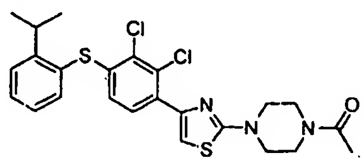
Furan-2-ylmethyl-(4-(4-(2-isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-thiazol-2-yl)-amine **38** was synthesized according to the following procedure.



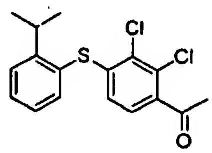
The title compound was prepared according to the procedure of Example 3 from compound **25** (20 mg, 0.05 mmole) and N-furfuryl thiourea (16 mg, 0.1 mmole). Yield: 9.4 mg, 40.0%. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.18 (d, J= 8.5 Hz, 6H), 3.51 (heptet, J=5.5 Hz, 1H), 4.53 (s, 2H), 6.34 (s, 2H), 6.71 (s, 1H), 6.90 (d, J=10.5 Hz, 1H), 7.18-7.21 (m, 1H), 7.38-7.43 (m, 4H), 7.70 (d, J=10.5 Hz, 1H), 8.07 (d, J=2.0 Hz, 1H). MS (DCI/NH_3) m/z 475 $(M+H)^+$.

Example 11

1-(4-(4-(2,3-Dichloro-4-(2-isopropyl-phenylsulfanyl)-phenyl)-thiazol-2-yl)-piperazin-1-yl)-ethanone **39** was synthesized according to the following procedure.



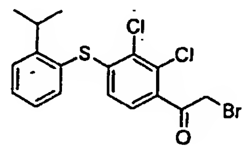
39



40

11A. First, 1-(2,3-dichloro-4-(2-isopropyl-phenylsulfanyl)-phenyl)-ethanone **40** was prepared as follows. To a solution of o-isopropyl thiophenol (3.14 g, 25 mmole) and 2,3,4-trichloro-acetophenone (5.9 g, 25 mmole) in DMF (100 ml) was added Na_2CO_3 (2.65 g, 25 mmole). The reaction was quenched with water (300 ml) after stirring for 50 hours at ambient temperature. The solution was extracted with EtOAc (3x100 ml). The combined EtOAc solution was dried ($MgSO_4$), filtered and concentrated. The residue

was chromatographed on a silica gel column, eluting with 10% EtOAc in hexane, giving the title compound **40** as a white solid, 3.4 g, 40.5%. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.19 (d, J= 8.5 Hz, 6H), 2.66 (s, 3H), 3.43 (heptaplet, J=8.5 Hz, 1H), 6.42 (d, J=8.4 Hz, 1H), 7.19 (d, J=8.4 Hz, 1H), 7.25-7.30 (m, 1H), 7.48-7.53 (m, 3H). MS (DCI/NH_3) m/z 339, 341 $(M+H)^+$; 356, 358 $(M+NH_4)^+$.



41

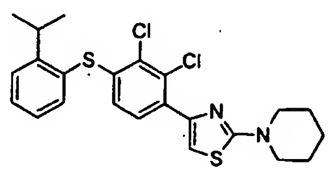
11B. Then 2-bromo-1-(2,3-dichloro-4-(2-isopropyl-phenylsulfanyl)-phenyl)-ethanone **41** was prepared as follows. A solution of Br_2 (50 mg) in dioxane (1.0 ml) was added to a solution of compound **40** (100 mg, 0.3 mmole) in 2 ml of dioxane. The solution was then stirred for another 10 minutes and concentrated. The residue was dissolved in EtOAc and purified on a 5-g silica gel cartridge, giving the desired product **41** as a white solid. 136 mg, ~100%. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.19 (d, J= 8.5 Hz, 6H), 3.43 (heptet, J=8.5 Hz, 1H), 4.45 (s, 2H), 6.42 (d, J=8.4 Hz, 1H), 7.19 (d, J=8.4 Hz, 1H), 7.25-7.31 (m, 1H), 7.49-7.54 (m, 3H); MS (DCI/NH_3) m/z 436 $(M+NH_4)^+$.

11C. A solution of compound **41** (30 mg, 0.07 mmole) and 1-thiocarbamyl-4-acetyl piperazine (20.5 mg, 0.11 mmole) in DMF (1.0 ml) was stirred at ambient temperature for two hours. The solvent was evaporated and the residue was purified on a 5-g silica gel cartridge, giving the desired product **39** as a white solid. 23 mg, 65.7%. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.19 (d, J= 8.5 Hz, 6H), 2.14 (s, 3H), 3.46-3.60 (m, 7H),),

3.75-3.78 (m, 2H), 6.48 (d, J=8.4 Hz, 1H), 7.09 (s, 1H), 7.21 (m, 1H), 7.44-7.51 (m, 3H), 7.57 (d, J=8.4 Hz, 1H). MS (DCI/NH_3) m/z 506 $(M+H)^+$.

Example 12

1-(4-(2,3-Dichloro-4-(2-isopropyl-phenylsulfanyl)-phenyl)-thiazol-2-yl)-piperadine **42** was synthesized according to the following procedure.

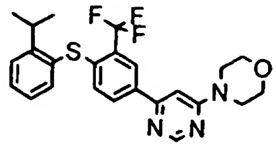


42

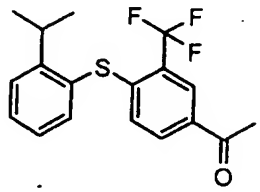
The title compound **42** was prepared according to the procedure of Example 11 from compound **41** (30 mg, 0.07 mmole) and 1-thiocarbamyl piperidine. Yield: 21 mg, 65.6%. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.19 (d, J= 8.5 Hz, 6H), 1.65 (m, 6H), 3.44-3.52 (m, 5H),), 6.48 (d, J=8.4 Hz, 1H), 7.01 (s, 1H), 7.21 (m, 1H), 7.44-7.51 (m, 3H), 7.61 (d, J=8.4 Hz, 1H). MS (DCI/NH_3) m/z 463 $(M+H)^+$.

Example 13

4-(6-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-yl)-morpholine **43** was synthesized according to the following procedure.

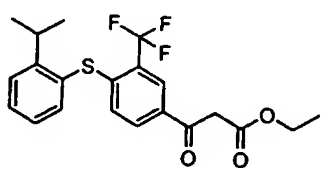


43



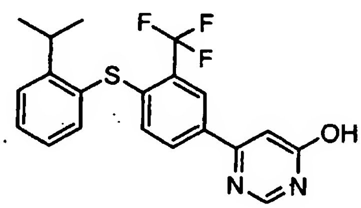
44

13A First, 1-(4-(2-isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-ethanone **44** was prepared as follows. To a solution of 4-fluoro-3-trifluoromethyl-acetophenone (7.00 g, 34.0 mmol) in DMF (100 mL) was added 2-isopropylthiophenol (6.33 g, 37.4 mmol) followed by cesium carbonate (16.6 g, 51.0 mmol). The mixture was stirred at room temperature overnight. The reaction was partitioned between ethyl acetate (250 mL) and water (250 mL). The organic layer was separated, washed with brine (5x250 mL), dried over $MgSO_4$ and filtered. After evaporating the solvent, the crude material was loaded to a silica gel column, eluting with 5% ethyl acetate in hexane to give a colorless oil **44** (11.5g, 100%). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.17 (d, J = 6.7 Hz, 6H), 2.57 (s, 3H), 3.46 (heptete, J = 6.8 Hz, 1H), 6.80 (d, J = 8.5Hz, 1H), 7.24-7.29 (m, 1H), 7.45-7.50 (m, 2H), 7.53 (d, J = 7.5Hz, 1H), 7.79 (dd, J = 2.0Hz, 8.5Hz, 1H), 8.21 (d, J = 1.4 Hz, 1H). MS (DCI) m/z 339 $(M+H)^+$; 356 $(M+NH_4)^+$.



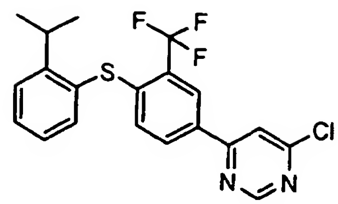
45

13B. Then, 3-(4-(2-isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-3-oxo-propionic acid ethyl ester **45** was prepared as follows. To a solution of compound 44 (11.5 g, 34.0 mmol) in THF (150 mL) was added 60% sodium hydride in mineral oil (1.84 g, 40.8 mmol). The mixture was stirred at room temperature for 10 minutes. Diethyl carbonate (46.5 mL, 340 mmol) was added and the mixture was heated under reflux for 2 hours. 10% HCl aq. (100 mL) was added and the solution was extracted with ethyl acetate (200 mL). The organic layer was separated, washed with brine (5x250 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated on a rotor-vapor to give a brown oil **45** (10.6 g, 76%); MS (DCI) m/z 411 $(M+H)^+$; 428 $(M+NH_4)^+$.



46

13C. Then, 6-(4-(2-isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-ol 46 was prepared as follows. The mixture of compound **45** (10.6 g, 25.8 mmol) and formamidine hydrochloride (10.4 g, 129 mmol) in 20% HOAc in DMF (50 mL) was heated at 120 °C for 3 days. MeOH (50 mL) was added and the resulting solution was purified on a preparative HPLC column, C_8 reverse-phase column, eluted with NH_4OAc-H_2O-CH_3CN. Evaporation of solvents gave a white solid **46** (1.40 g, 14%); MS (APCI) m/z 391 $(M+H)^+$.



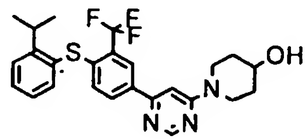
47

13D. Then, 4-chloro-6-(4-(2-isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidine **47** was prepared as follows. Compound **46** (1.40 g, 3.59 mmol) was treated with $POCl_3$ (30 mL) at 60 °C for an hour. The reaction mixture was concentrated on a rotor-vapor, and the residue was treated with crushed ice (10 g). Water (50 mL) was added. The aqueous solution was then extracted with ethyl acetate (2x50 mL). The combined organic layers were washed with brine (3x50 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified by chromatography to give a brown oil **47** (0.74 g, 51%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.19 (d, J = 6.7 Hz, 6H), 3.50 (heptet, J = 6.8 Hz, 1H), 6.89 (d, J = 8.5 Hz, 1H), 7.24-7.28 (m, 1H), 7.46-7.50 (m, 2H), 7.54 (d, J = 7.6 Hz, 1H), 7.68 (s, 1H), 7.93 (d, J = 8.4 Hz, 1H), 8.38 (s, 1H), 9.00(s, 1H). MS (DCI) m/z 409, 411 $(M+H)^+$.

13E. To a solution of compound **47** (0.015g, 0.0367 mmol) in DMF (1.0 mL) was added morpholine followed by potassium carbonate (0.015g, 0.109 mmol). The reaction mixture was heated at 80°C for 16 hours. The solid was removed through filtration, and the filtrate was directly purified by preparative HPLC, to give a yellow solid, **43** (0.012 g, 72%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.19 (d, J = 6.8 Hz, 6H), 3.51 (heptet, J = 6.8 Hz, 1H), 3.69 (t, J = 4.9 Hz, 4H), 3.81 (t, J = 4.9 Hz, 4H), 6.80 (s, 1H), 6.90 (d, J = 8.5 Hz, 1H), 7.20-7.24 (m, 1H), 7.43 (s, 1H), 7.44 (s, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.87 (d, J = 8.2 Hz, 1H), 8.26 (s, 1H), 8.67(s, 1H). MS (APCI) m/z 460 $(M+H)^+$.

Example 14

1-(6-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-yl)-piperidin-4-ol **48** was synthesized according to the following procedure.

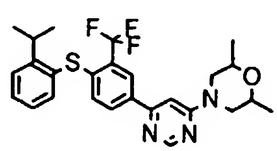


48

The title compound **48** was prepared according to the procedures of Example 13E, substituting morpholine with 4-hydroxypiperidine. A yellow solid was obtained (0.012 g, 71%). ^{1}H-NMR (DMSO, 400 MHz) δ 1.14 (d, J = 7.2 Hz, 6H), 1.48-1.52 (m, 2H), 1.87-1.90 (m, 2H), 3.10-3.70 (m, 4H, overlapping with the solvent H_2O peak), 4.38-4.42 (m, 2H), 6.90 (d, J = 8.4 Hz, 1H), 7.32-7.35 (m, 2H), 7.47-7.55 (m, 3H), 8.25 (d, J=8.2 Hz, 1H), 8.50 (s, 1H), 8.55 (s, 1H); MS (APCI) m/z 474 $(M+H)^+$.

Example 15

4-(6-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-yl)-2,6-dimethyl-morpholine **49** was synthesized according to the following procedure.

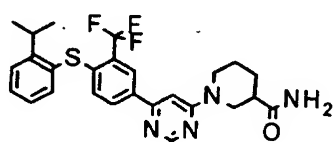


49

The title compound was prepared according to the procedures of Example 13E, substituting morpholine with 2,6-dimethylmorpholine. A yellow solid **49** was obtained (0.013 g, 73%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.18 (d, J = 7.2 Hz, 6H), 1.28 (d, J = 6.4 Hz, 6H), 2.65 (dd, J = 2.1, 10.6 Hz, 2H), 3.52 (heptet, J = 6.8 Hz, 1H), 3.65-3.70 (m, 2H), 4.24 (br d, J = 11.5 Hz, 2H), 6.78 (s, 1H), 6.90 (d, J = 8.4 Hz, 1H), 7.20-7.24 (m, 1H), 7.43 (s, 1H), 7.44 (s, 1H), 7.48 (d, J = 7.7 Hz, 1H), 7.87 (d, J = 8.5 Hz, 1H), 8.27 (s, 1H), 8.66(s, 1H). MS (APCI) m/z 488 $(M+H)^+$.

Example 16

1-(6-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-yl)-piperidine-3-carboxylic acid amide **50** was synthesized according to the following procedure.



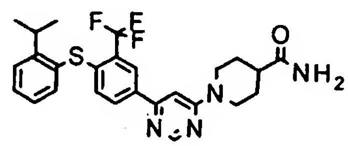
50

The title compound was prepared according to the procedures of Example 13E, substituting morpholine with nipecotamide. A yellow solid **50** was obtained (0.014 g, 74%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.19 (d, J = 6.8 Hz, 6H), 1.54-1.66 (m 1H), 1.76-1.84 (m, 1H), 1.96-2.12 (m, 2H), 2.46-2.53 (m, 1H), 3.27-3.35 (m, 1H), 3.51 (heptaplet, J = 6.6 Hz, 1H), 3.70-3.76 (m, 1H), 3.94-4.01 (br, 1H), 4.20-4.26 (m, 1H), 5.44 (s, br, 1H), 6.10 (s, br, 1H), 6.84 (s, 1H), 6.90 (d, J = 8.1 Hz, 1H), 7.20-7.25 (m, 1H), 7.43 (s, 1H),

7.44 (s, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 8.28 (s, 1H), 8.64 (s, 1H). MS (APCI) m/z 501 $(M+H)^+$.

Example 17

1-(6-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-yl)-piperidine-4-carboxylic acid amide **51** was synthesized according to the following procedure.

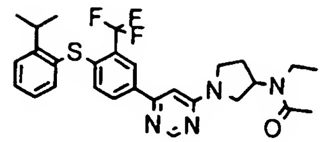


51

The title compound was prepared according to the procedures of Example 13E, substituting morpholine with *iso*-nipecotamide. A yellow solid **51** was obtained (0.013g, 69%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.19 (d, J = 6.8 Hz, 6H), 1.71-1.82 (m, 2H), 1.97-2.04 (m, 2H), 2.44-2.53 (m, 1H), 3.07 (t, J = 12.5 Hz, 2H), 3.52 (heptet, J = 6.8 Hz, 1H), 4.49 (d, J = 13.6 Hz, 2H), 5.49 (br s, 1H), 5.59 (br s, 1H), 6.83 (s, 1H), 6.90 (d, J = 8.5 Hz, 1H), 7.20-7.24 (m, 1H), 7.43 (s, 1H), 7.44 (s, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.86 (d, J = 8.5 Hz, 1H), 8.26 (s, 1H), 8.65 (s, 1H); MS (APCI) m/z 501 $(M+H)^+$.

Example 18

N-Ethyl-N-1-(6-(4-(2-isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-yl)-pyrrolidin-3-yl)-acetamide **52** was synthesized according to the following procedure.

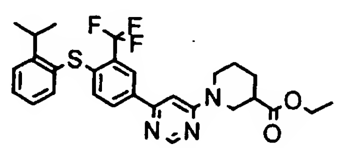


52

The title compound was prepared according to the procedures of Example 13E, substituting morpholine with 3-(N-acetyl-N-ethylamino)pyrrolidine. A yellow solid **52** was obtained (0.014 g, 72%). MS (APCI) m/z 529 $(M+H)^+$.

Example 19

1-(6-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-yl)-piperidine-3-carboxylic acid ethyl ester **53** was synthesized according to the following procedure.



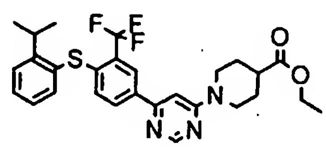
53

The title compound was prepared according to the procedures of Example 13E, substituting morpholine with ethyl nipecotate. A yellow solid **53** was obtained (0.011 g, 56%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.19 (d, J = 6.7 Hz, 6H), 1.25 (t, J = 7.2 Hz, 3H), 1.57-1.60 (m, 1H), 1.79-1.88 (m, 2H), 2.10-2.14 (m, 1H), 2.54-2.59 (m, 1H), 3.21-3.38 (m, 1H), 3.35-3.40 (m, 1H), 3.52 (heptet, J = 6.8 Hz, 1H), 4.11-4.18 (m, 1H), 4.16 (q, J = 7.2, 2H), 4.38-4.44 (m, 1H), 6.86 (s, 1H), 6.90 (d, J = 8.5 Hz, 1H), 7.20-7.25 (m, 1H),

7.43 (s, 1H), 7.44 (s, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 8.28 (s, 1H), 8.65 (s, 1H); MS (APCI) m/z 530 $(M+H)^+$.

Example 20

1-(6-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-yl)-piperidine-4-carboxylic acid ethyl ester 54 was synthesized according to the following procedure.

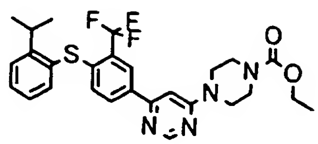


54

The title compound was prepared according to the procedures of Example 13E, substituting morpholine with ethyl isonipecotate. A yellow solid 54 was obtained (0.012 g, 61%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.19 (d, J = 6.8 Hz, 6H), 1.27 (t, J = 7.2 Hz, 3H), 1.71-1.81 (m, 2H), 2.00-2.04 (m, 2H), 2.58-2.65 (m, 1H), 3.11-3.18 (m, 2H), 3.52 (heptet, J = 6.8 Hz, 1H), 4.16 (q, J = 7.2 Hz, 2H), 4.32-4.38 (m, 2H), 6.82 (s, 1H), 6.90 (d, J = 8.5 Hz, 1H), 7.20-7.24 (m, 1H), 7.43 (s, 1H), 7.44 (s, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.86 (d, J = 8.5 Hz, 1H), 8.26 (s, 1H), 8.65 (s, 1H); MS (APCI) m/z 530 $(M+H)^+$.

Example 21

4-(6-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-yl)-piperazine-1-carboxylic acid ethyl ester 55 was synthesized according to the following procedure.

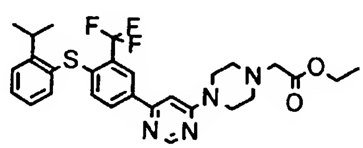


55

The title compound was prepared according to the procedures of Example 13E, substituting morpholine with ethyl piperazine-1-carboxylate. A yellow solid **55** was obtained (0.019 g, 96%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.19 (d, J = 6.8 Hz, 6H), 1.29 (t, J = 7.2 Hz, 3H), 3.51 (heptaplet, J = 6.8 Hz, 1H), 3.59-3.62 (m, 4H), 3.71-3.75 (m, 4H), 4.19 (q, J = 7.2 Hz, 2H), 6.81 (s, 1H), 6.90 (d, J = 8.5 Hz, 1H), 7.19-7.25 (m, 1H), 7.42-7.45 (m, 2H), 7.46-7.50 (m, 1H), 7.86 (d, J = 8.5 Hz, 1H), 8.26 (s, 1H), 8.67 (s, 1H); MS (APCI) m/z 531 $(M+H)^+$.

<u>Example 22</u>

4-(6-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-yl)-piperazin-1-yl)-acetic acid ethyl ester **56** was synthesized according to the following procedure.



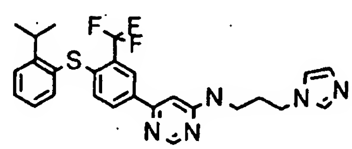
56

The title compound was prepared according to the procedures of Example 13E, substituting morpholine with 1-(ethoxycarbonylmethyl)piperazine. A yellow solid **56**

was obtained (0.007 g, 37%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.18 (d, J = 6.8 Hz, 6H), 1.29 (t, J = 7.2 Hz, 3H), 2.70 (br, 4H), 3.28 (s, 2H), 3.51 (heptet, J = 6.8 Hz, 1H), 3.78 (br m, 4H), 4.21 (q, J = 7.2 Hz, 2H), 6.80 (s, 1H), 6.90 (d, J = 8.5 Hz, 1H), 7.21-7.27 (m, 1H), 7.42-7.45 (m, 2H), 7.46-7.50 (m, 1H), 7.86 (d, J = 8.5 Hz, 1H), 8.26 (s, 1H), 8.65 (s, 1H); MS (APCI) m/z 545 $(M+H)^+$.

Example 23

(3-Imidazol-1-yl-propyl)-(6-(4-(2-isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-yl)-amine **57** was synthesized according to the following procedure.

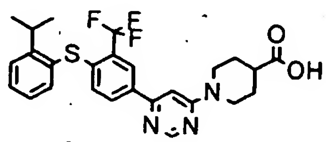


57

The title compound was prepared according to the procedures of Example 13E, substituting morpholine with 1-(3-aminopropyl)imidazole. A yellow solid **57** was obtained (0.010 g, 54%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.18 (d, J = 6.8 Hz, 6H), 2.16 (p, J = 6.8 Hz, 2H), 3.36-3.41 (m, 2H), 3.51 (heptet, J = 6.8 Hz, 1H), 4.10 (t, J = 6.7, 2H), 6.58 (s, 1H), 6.89 (d, J = 8.5 Hz, 1H), 6.95 (s, 1H), 7.09 (s, 1H), 7.21-7.25 (m, 1H), 7.43-7.46 (m 2H), 7.49 (d, J = 7.6 Hz, 1H), 7.60 (s, 1H), 7.83 (d, J = 8.4Hz, 1H), 8.26 (s, 1H), 8.58 (s, 1H). MS (APCI) m/z 498 $(M+H)^+$.

Example 24

1-(6-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-yl)-piperidine-4-carboxylic acid **58** was synthesized according to the following procedure.

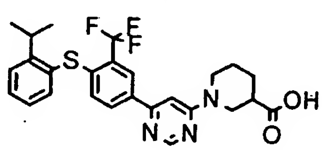


58

The title compound was prepared according to the procedures of Example 13E, substituting morpholine with isonipecotic acid. A yellow solid **58** was obtained (0.004 g, 24%). ^{1}H-NMR (DMSO, 400 MHz) δ 1.14 (d, J = 7.2 Hz, 6H), 1.48-1.52 (m, 2H), 1.87-1.90 (m, 2H), 3.10-3.70 (m, 4H, overlapping with the solvent H_2O peak), 4.38-4.42 (m, 2H), 6.90 (d, J = 8.4 Hz, 1H), 7.31-7.35 (m, 2H), 7.47-7.55 (m, 3H), 8.25 (d, J=8.2 Hz, 1H), 8.50 (s, 1H), 8.55 (s, 1H). MS (APCI) m/z 502 $(M+H)^+$.

Example 25

1-(6-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-yl)-piperidine-3-carboxylic acid **59** was synthesized according to the following procedure.

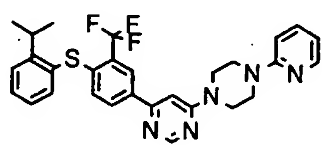


59

The title compound was prepared according to the procedures of Example 13E, substituting morpholine with nipecotic acid. A yellow solid **59** was obtained (0.011 g, 57%). ^{1}H-NMR (DMSO, 400 MHz) δ 1.14 (d, J = 7.2 Hz, 6H), 1.43-1.46 (m, 2H), 1.63-1.72 (m, 2H), 1.97-1.20 (m, 1H), 2.36-2.41 (m, 1H), 3.10-3.70 (m, 2H, overlapping with the solvent H_2O peak), 4.24-4.28 (m, 1H), 4.46-4.52 (m, 1H), 6.90 (d, J = 8.4 Hz, 1H), 7.30-7.33 (m, 1H), 7.38 (s, 1H), 7.46 (d, J=8.0 Hz, 1H), 7.48-7.57 (m, 2H), 8.25 (d, J=8.2 Hz, 1H), 8.50 (s, 1H), 8.55 (s, 1H); MS (APCI) m/z 502 $(M+H)^+$.

Example 26

4-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-yl)-piperidine-3-carboxylic acid **60** was synthesized according to the following procedure.

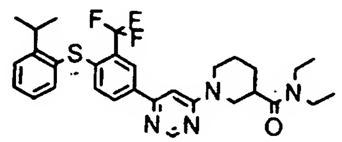


60

The title compound was prepared according to the procedures of Example 13E, substituting morpholine with 1-(2-pyridyl)piperazine. A yellow solid **60** was obtained (0.013 g, 65%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.19 (d, J = 6.8 Hz, 6H), 3.52 (heptet, J = 6.8 Hz, 1H), 3.71 (t, J = 5.3 Hz, 4H), 3.87 (t, J = 5.3 Hz, 4H), 6.66-6.69 (m, 2H), 6.84 (s, 1H), 6.90 (d, J = 8.5 Hz, 1H), 7.21-7.25 (m, 1H), 7.43 (s, 1H), 7.44 (s, 1H), 7.47-7.55 (m, 2H), 7.88 (d, J = 8.5 Hz, 1H), 8.21-8.23 (m, 1H), 8.29 (s, 1H), 8.68 (s, 1H); MS (APCI) m/z 536 $(M+H)^+$.

Example 27

1-(6-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-yl)-piperidine-3-carboxylic acid diethylamide **61** was synthesized according to the following procedure.

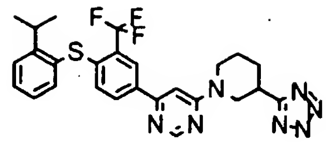


61

The title compound was prepared according to the procedures of Example 13E, substituting morpholine with *N,N*-diethyl nipecotamide. A yellow solid **61** was obtained (0.014 g, 69%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.13 (t, J = 7.2 Hz, 3H), 1.19 (d, J = 6.8 Hz, 6H), 1.21 (t, J = 7.2 Hz, 3H), 1.52-1.59 (m, 1H), 1.82-1.99 (m, 3H), 2.61-2.69 (m, 1H), 3.30 (m, 1H), 3.15 (m, 1H), 3.32-3.45 (m, 4H), 3.52 (heptet, J = 6.8 Hz, 1H), 4.35-4.41 (br, 1H), 4.58-4.65 (br, 1H), 6.82 (s, 1H), 6.90 (d, J = 8.5 Hz, 1H), 7.21-7.24 (m, 1H), 7.43 (s, 1H), 7.44 (s, 1H), 7.48 (d, J = 7.7 Hz, 1H), 7.85 (d, J = 8.5 Hz, 1H), 8.26 (s, 1H), 8.63 (s, 1H); MS (DCI) m/z 557 $(M+H)^+$.

Example 28

4-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-6-(3-(2*H*-tetrazol-5-yl)-piperidin-1-yl)-pyrimidine **62** was synthesized according to the following procedure.

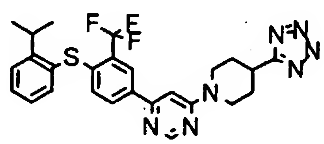


62

The title compound was prepared according to the procedures of Example 13E, substituting morpholine with 3-(5'-tetrazolyl)-piperidine. A yellow solid **62** was obtained (0.004 g, 21%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.18 (d, J = 6.8 Hz, 6H), 1.45-1.56 (m, 1H), 1.68-1.77 (m, 1H), 2.17-2.27 (m, 1H), 2.51-2.59 (m, 1H), 3.42-3.51 (m, 2H), 3.50 (heptaplet, J = 6.8 Hz, 1H), 3.66-3.73 (m, 1H), 3.92-3.98 (m, 1H), 4.51-4.57 (m, 1H), 6.86-6.91 (m, 2H), 7.21-7.28 (m, 1H), 7.43-7.51 (m, 3H), 7.85 (d, J = 8.5 Hz, 1H), 8.23 (s, 1H), 8.78 (s, 1H); MS (APCI) m/z 526 $(M+H)^+$.

Example 29

4-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-6-(4-(2*H*-tetrazol-5-yl)-piperidin-1-yl)-pyrimidine **63** was synthesized according to the following procedure.



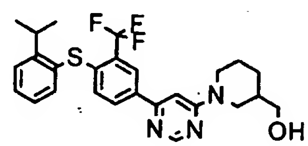
63

The title compound was prepared according to the procedures of Example 13E, substituting morpholine with 4-(5'-tetrazolyl)-piperidine. A yellow solid **63** was obtained (0.008 g, 40%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.17 (d, J = 6.8 Hz, 6H), 1.78-182 (m, 2H), 2.10-2.15 (m, 2H), 3.11-3.19 (m, 2H), 3.29-3.37 (m, 1H), 3.49 (heptet, J = 6.8 Hz,

1H), 4.43-4.49 (br, 2H), 6.82 (s, 1H), 6.88 (d, J = 8.5 Hz, 1H), 7.18-7.25 (m, 1H), 7.42 (s, 1H), 7.43 (s, 1H), 7.46 (d, J = 7.7 Hz, 1H), 7.81 (d, J = 8.5 Hz, 1H), 8.21 (s, 1H), 8.61 (s, 1H); MS (APCI) m/z 526 $(M+H)^+$.

Example 30

(1-(6-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-yl)-piperidin-3-yl)-methanol **64** was synthesized according to the following procedure.

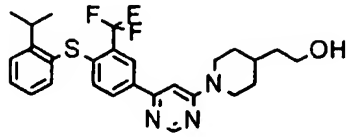


64

The title compound was prepared according to the procedures of Example 13E, substituting morpholine with 3-hydroxymethyl piperidine. A yellow solid **64** was obtained (0.012 g, 67%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.17 (d, J = 6.8 Hz, 6H), 1.78-182 (m, 2H), 2.10-2.15 (m, 2H), 3.11-3.19 (m, 2H), 3.29-3.37 (m, 1H), 3.49 (heptaplet, J = 6.8 Hz, 1H), 4.43-4.49 (br, 2H), 6.82 (s, 1H), 6.88 (d, J = 8.5 Hz, 1H), 7.18-7.25 (m, 1H), 7.42 (s, 1H), 7.43 (s, 1H), 7.46 (d, J = 7.7 Hz, 1H), 7.81 (d, J = 8.5 Hz, 1H), 8.21 (s, 1H), 8.61 (s, 1H); MS (APCI) m/z 488 $(M+H)^+$.

Example 31

2-(1-(6-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-yl)-piperidin-4-yl)-ethanol **65** was synthesized according to the following procedure.

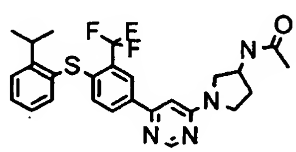


65

The title compound was prepared according to the procedures of Example 13E, substituting morpholine with 4-(2'-hydroxyethyl)-piperidine. A yellow solid **65** was obtained (0.013 g. 68%). ^{1}H-NMR (DMSO, 400 MHz) δ 1.06-1.09 (m, 1H), 1.14 (d, J = 7.2 Hz, 6H), 1.37-1.38 (m, 2H), 1.73-1.75 (m, 3H), 2.90 (t, J=10.8 Hz, 1H), 3.74-3.48 (m, 3H), 4.35-4.37 (m, 1H), 4.51-4.54 (m, 1H), 6.90 (d, J = 8.4 Hz, 1H), 7.30-7.33 (m, 2H), 7.46 (d, J=8.0 Hz, 1H), 7.48-7.57 (m, 2H), 8.25 (d, J=8.2 Hz, 1H), 8.50 (s, 1H), 8.53 (s, 1H); MS (APCI) m/z 502 $(M+H)^+$.

Example 32

N-(1-(6-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-yl)-pyrrolidin-3-yl)-acetamide **66** was synthesized according to the following procedure.



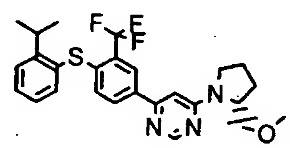
66

The title compound was prepared according to the procedures of Example 13E, substituting morpholine with 3-acetamidopyrrolidine. A yellow solid **66** was obtained (0.012 g, 67%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.19 (d, J = 6.8 Hz, 6H), 2.00 (s, 3H), 2.02-2.08 (m, 1H), 2.30-2.39 (m, 1H), 3.38-3.52 (br, 1H), 3.51 (heptet, J = 6.8 Hz, 1H),

3.60-3.70 (br, 1H), 3.78-3.87 (m, 1H), 4.58-4.66 (m, 1H), 5.62-5.68 (m, 1H), 6.59 (s, 1H), 6.90 (d, J = 8.5 Hz, 1H), 7.20-7.28 (m, 1H), 7.43 (s, 1H), 7.44 (s, 1H), 7.48 (d, J = 7.7 Hz, 1H), 7.88 (d, J = 8.5 Hz, 1H), 8.28 (s, 1H), 8.65 (s, 1H); MS (APCI) m/z 501 $(M+H)^+$.

Example 33

4-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-6-(2-methoxymethyl-pyrrolidin-1-yl)-pyrimidine **67** was synthesized according to the following procedure.

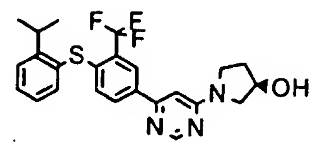


67

The title compound was prepared according to the procedures of Example 13E, substituting morpholine with (R)-(+)-2-(methoxymethyl)pyrrolidine. A yellow solid **67** was obtained (0.011 g, 63%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.19 (d, J = 6.8 Hz, 6H), 2.01-2.15 (m, 4H), 3.36 (s, 3H), 3.38-3.62 (m, 4H), 3.52 (heptet, J = 6.8 Hz, 1H), 4.36 (s, br, 1H), 6.68 (s, 1H), 6.91 (d, J = 8.5 Hz, 1H), 7.18-7.26 (m, 1H), 7.43 (s, 1H), 7.44 (s, 1H), 7.47 (d, J = 7.7 Hz, 1H), 7.86 (d, J = 8.5 Hz, 1H), 8.28 (s, 1H), 8.64 (s, 1H); MS (APCI) m/z 488 $(M+H)^+$.

Example 34

1-(6-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-yl)-pyrrolidin-3-ol **68** was synthesized according to the following procedure.

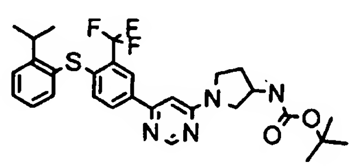


68

The title compound was prepared according to the procedures of Example 13E, substituting morpholine with (R)-(+)-3-pyrrolidinol. A yellow solid **68** was obtained (0.012 g, 73%). ^{1}H-NMR (DMSO, 400 MHz) δ1.14 (d, J = 7.2 Hz, 6H), 1.80-2.10 (m, 2H), 3.43 (heptet, 7.2 Hz, 1H), 3.54 (br s, 3H), 4.22 (m, 1H), 5.10 (m, 1H), 6.92 (d, J = 8.4 Hz, 1H), 7.01 (s, 1H), 7.31-7.35 (m, 1H), 7.47 (d, J=8.0 Hz, 1H), 7.48-7.57 (m, 2H), 8.25 (d, J=8.2 Hz, 1H), 8.50 (s, 1H), 8.52 (s, 1H); MS (APCI) m/z 460 $(M+H)^+$.

Example 35

(1-(6-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-yl)-pyrrolidin-3-yl)-carbamic acid *tert*-butyl ester **69** was synthesized according to the following procedure.



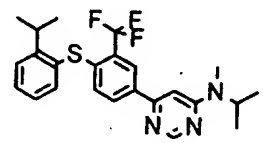
69

The title compound was prepared according to the procedures of Example 13E, substituting morpholine with 3-(tert-butoxycarbonylamino)pyrrolidine. A yellow solid **69** was obtained (0.015 g, 72%). ^{1}H-NMR (DMSO, 400 MHz) δ1.14 (d, J = 7.2 Hz, 6H),

1.39 (s, 9H), 1.90 (br s, 1H), 2.18 (br s, 1H), 3.43 (heptet, 7.2 Hz, 1H), 3.54 (br s, 4H), 4.18 (m, 1H), 6.91 (d, J = 8.4 Hz, 1H), 7.02 (s, 1H), 7.22 (br s, 1H), 7.31-7.35 (m, 1H), 7.47 (d, J=8.0 Hz, 1H), 7.48-7.57 (m, 2H), 8.25 (d, J=8.2 Hz, 1H), 8.50 (s, 1H), 8.52 (s, 1H); MS (APCI) m/z 459 $(M+H)^+$.

Example 36

Isopropyl-(6-(4-(2-isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-yl)-methyl amine **70** was synthesized according to the following procedure.

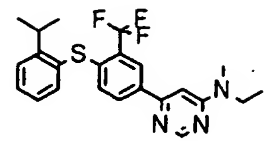


70

The title compound was prepared according to the procedures of Example 13E, substituting morpholine with N-methylisopropylamine. A yellow solid **70** was obtained (0.009 g, 57%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.19 (d, J = 6.8 Hz, 6H), 1.22 (d, J = 6.8 Hz, 6H), 2.93 (s, 3H), 3.52 (heptaplet, J = 6.8 Hz, 1H), 6.69 (s, 1H), 6.91 (d, J = 8.5 Hz, 1H), 7.19-7.24 (m, 1H), 7.42 (s, 1H), 7.43 (s, 1H), 7.48 (d, J = 7.7 Hz, 1H), 7.86 (d, J = 8.5 Hz, 1H), 8.27 (s, 1H), 8.64 (s, 1H). MS (APCI) m/z 446. $(M+H)^+$.

Example 37

Ethyl-(6-(4-(2-isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-yl)-methyl-amine **71** was synthesized according to the following procedure.

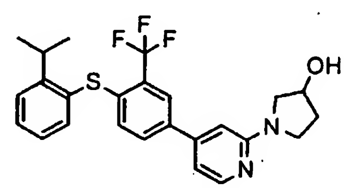


71

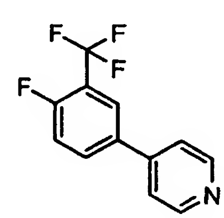
The title compound was prepared according to the procedures of Example 13E, substituting morpholine with N-ethylmethylamine. A yellow solid **71** was obtained (0.009 g, 56%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.19 (d, J = 6.8 Hz, 6H), 1.21 (t, J = 7.2 Hz, 3H), 3.11 (s, 3H), 3.52 (heptet, J = 6.8 Hz, 1H), 3.64 (q, J = 7.2 Hz, 2H), 6.68 (s, 1H), 6.91 (d, J = 8.5 Hz, 1H), 7.19-7.24 (m, 1H), 7.42 (s, 1H), 7.43 (s, 1H), 7.47 (d, J = 7.7 Hz, 1H), 7.86 (d, J = 8.5 Hz, 1H), 8.28 (s, 1H), 8.64 (s, 1H). MS (APCI) m/z 432 $(M+H)^+$.

Example 38

1-(4-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-pyrrolidin-3-ol **72** was synthesized according to the following procedure.

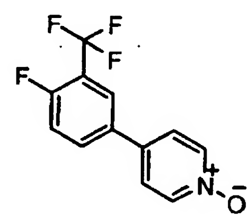


72



73

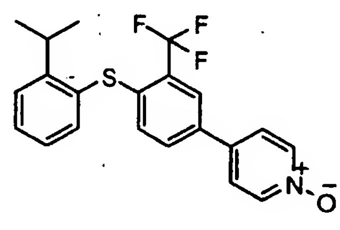
38A. First, 4-(4-fluoro-3-trifluoromethyl-phenyl)-pyridine **73** was prepared as follows. To a suspension of pyridine-4-boronic acid (2.59 g, 21.1 mmol) in 1-propanol (60 mL) was added 5-bromo-2-fluorobenzotrifluoride (5.12 g, 21.1 mmol) and triphenylphosphine (0.160 g, 0.610 mmol), followed by sodium carbonate in water (2.0 M, 12 mL). The mixture was purged with nitrogen gas for 10 minutes. To it was added palladium(II) acetate (0.044 g, 0.196 mmol) and it was then heated under reflux for 4 hours. The reaction mixture was partitioned between ethyl acetate (200 mL) and water (200 mL). The organic layer was separated, washed with brine (3x200 mL), dried over $MgSO_4$, then filtered. After evaporating the solvent, the crude material was loaded to a silica gel column, eluting with 60% ethyl acetate in hexane to give a white solid **73** (2.73 g, 54%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.34-7.42 (m, 1H), 7.61-7.65 (m, 2H), 7.80-7.93 (m, 2H), 8.73-8.84 (m, 2H); MS (DCI) m/z 242, 243 $(M+H)^+$.



74

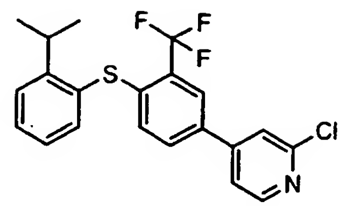
38B. Then, 4-(4-fluoro-3-trifluoromethyl-phenyl)-pyridine-1-oxide **74** was prepared as follows. To a solution of compound **73** (2.49 g, 10.3 mmol) in dichloromethane (10 mL) was added methyltrioxorhenium(VII) (0.128g, 0.515 mmol), followed by hydrogen peroxide in water (30%, 5.15 mL). The reaction mixture was stirred at room temperature for 16 hours. Manganese (IV) oxide (0.050g) was added. The mixture was stirred for another 30 minutes. The organic layer was separated. The aqueous layer was extracted with more dichloromethane (2x10 mL). The combined

organic phase was washed with brine (3x30 mL), dried over $MgSO_4$ and filtered. After evaporating the solvent, the crude material was loaded to a silica gel column, eluting with 10% methanol in ethyl acetate to give a white solid **74** (2.51g, 94%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.35 (t, J = 9.3 Hz, 1H), 7.49 (d, J = 7.2 Hz, 2H), 7.74-7.82 (m, 2H), 8.30 (d, J = 7.1 Hz, 2H); MS (DCI) m/z 258, 259 $(M+H)^+$.



75

38C. Then, 4-(4-(2-isopropyl-phenylsulfanyl-3-trifluoromethyl-phenyl)-pyridine-1-oxide **75** was prepared as follows. A solution of compound **74** (2.51g, 9.76 mmol) in dimethylacetamide (100 mL) was purged with nitrogen gas for 10 minutes. To it was added cesium carbonate (3.80 g, 11.7 mmol), followed by 2-isopropylthiophenol (4.90 mL, 29.3 mmol). The reaction was heated at 100 °C for 16 hours. The mixture was partitioned between ethyl acetate (200 mL) and water (200 mL). The organic layer was separated, washed with brine (5x200 mL), dried over $MgSO_4$ and then filtered. After evaporating the solvent, the crude material was loaded to a silica gel column, eluting with 10% methanol in ethyl acetate to give a white solid **75** (3.19 g 84%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.19 (d, J = 6.8 Hz, 6H), 3.51 (heptaplet, J = 6.8 Hz, 1H), 6.90 (d, J = 8.1 Hz, 1H), 7.22-7.28 (m, 1H), 7.44-7.51 (m, 6H), 7.84 (d, J = 2.1 Hz, 1H), 8.24 (d, J = 7.4 Hz, 2H); MS (DCI) m/z 390 $(M+H)^+$.



76

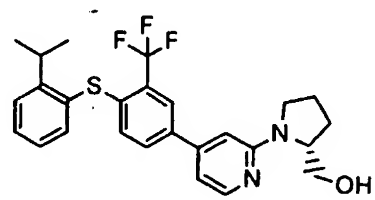
38D. Then, 2-chloro-4-(4-(2-isopropyl-phenylsulfanyl-3-trifluoromethyl-phenyl)-pyridine **76** was prepared as follows. Compound **75** (3.19 g, 8.19 mmol) was treated with $POCl_3$ (50 mL) at 100 °C for 10 hours. The reaction mixture was concentrated on a rotovap, and the residue was treated with crushed ice (20 g). Water (100 mL) was added, the aqueous solution was then extracted with ethyl acetate (2x100 mL). The combined organic layers were washed with brine (3x100 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified by chromatography to give the title compound **76** as a brown oil (2.74 g, 82%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.19 (d, J = 6.8 Hz, 6H), 3.51 (heptet, J = 6.8 Hz, 1H), 6.91 (d, J = 8.5 Hz, 1H), 7.25-7.28 (m, 1H), 7.37 (dd, J = 1.7 Hz, 5.1 Hz, 1H), 7.45-7.52 (m, 5H), 7.87 (d, J = 2.0 Hz, 1H), 8.43 (d, J = 5.4 Hz, 1H). MS (DCI) m/z 408, 409, 410 $(M+H)^+$.

38E. To a solution of compound **76** (0.024 g, 0.0588 mmol) in DMSO (0.50 mL) was added 3-hydroxylpyrrolidine (0.0256 g, 0.294 mmol). The reaction mixture was heated at 140°C for 16 hours. It was then cooled down to room temperature. Methanol was added to the reaction mixture and then purified by preparative HPLC to give a yellow solid **72** (0.0256 g, 95%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.20 (d, J = 6.8 Hz, 6H), 2.14-2.22 (m, 1H), 2.25-2.32 (m, 1H), 2.65 (s, 1H), 3.50 (heptet, J = 6.8 Hz, 1H), 3.75-3.83 (m, 2H), 3.86-3.94 (m, 2H), 4.73 (s, 1H), 6.78 (s, 1H), 6.91 (d, J = 8.0 Hz, 2H), 7.25-7.29

(m, 1H), 7.45-7.52 (m, 4H), 7.85 (d, J = 1.5 Hz, 1H), 8.10 (d, J = 7.0 Hz, 1H); MS (APCI) m/z 459 $(M+H)^+$.

Example 39

(1-(4-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-pyrrolidin-2-yl)-methanol **77** was synthesized according to the following procedure.

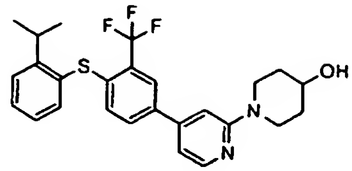


77

The title compound was prepared according to the procedures of Example 38E, substituting 3-hydroxypyrrolidine with (R)-2-(hydroxymethyl)pyrrolidine. A yellow solid **77** was obtained (0.0216 g, 78%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.20 (d, J = 6.8 Hz, 6H), 2.06-2.11 (m, 2H), 2.15-2.21 (m, 2H), 3.47-3.53 (m, 2H), 3.64-3.69 (m, 1H), 3.71-3.76 (m, 2H), 4.63 (s, 1H), 6.79 (s, 1H), 6.89-6.93 (m, 2H), 7.25-7.29 (m, 1H), 7.46-7.54 (m, 4H), 7.85 (d, J = 1.8 Hz, 1H), 8.10 (d, J = 6.9 Hz, 1H); MS (APCI) m/z 473 $(M+H)^+$.

Example 40

4'-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-3,4,5,6-tetrahydro-2*H*-(1,2')bipyridiny-4-ol **78** was synthesized according to the following procedure.

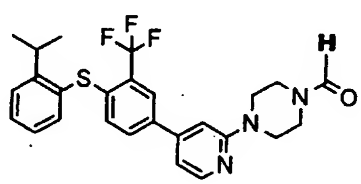


78

The title compound was prepared according to the procedures of Example 38E, substituting 3-hydroxypyrrolidine with 4-hydroxypiperidine. A yellow solid **78** was obtained (0.0255 g, 92%). ^{1}H-NMR (CDCl$_3$, 400 MHz) δ 1.20 (d, J = 6.8 Hz, 6H), 1.77-1.85 (m, 2H), 2.02-2.09 (m, 2H), 3.49 (heptet, J = 6.8 Hz, 1H), 3.68-3.74 (m, 2H), 3.99-4.06 (m, 2H), 4.12-4.16 (m, 1H), 6.90 (d, J = 8.0 Hz, 1H), 6.93 (d, J = 6.6 Hz, 1H), 6.98 (s, 1H), 7.25-7.29 (m, 1H), 7.46-7.54 (m, 4H), 7.85 (s, 1H), 8.19 (d, J = 6.6 Hz, 1H); MS (APCI) m/z 473 (M+H)$^+$.

Example 41

4-(4-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-piperazine-1-carbaldehyde **79** was synthesized according to the following procedure.



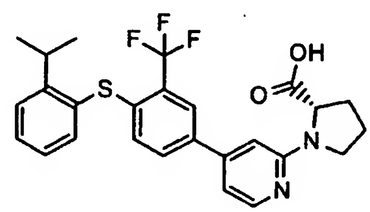
79

The title compound was prepared according to the procedures of Example 38E, substituting 3-hydroxypyrrolidine with 1-formylpiperazine. A yellow solid **79** was obtained (0.0073 g, 26%). ^{1}H-NMR (CDCl$_3$, 400 MHz) δ 1.19 (d, J = 6.8 Hz, 6H), 3.50

(heptet, J = 6.8 Hz, 1H), 3.62-3.66 (m, 2H), 3.69-3.73 (m, 2H), 3.75-3.78 (m, 2H), 3.89-3.93 (m, 2H), 6.92 (d, J = 8.5 Hz, 1H), 6.95 (s, 1H), 7.03 (d, J = 6.2 Hz, 1H), 7.25-7.29 (m, 1H), 7.46-7.54 (m, 4H), 7.85 (d, J = 1.8 Hz, 1H), 8.16 (s, 1H), 8.29 (d, J = 6.3 Hz, 1H); MS (APCI) m/z 486 $(M+H)^+$.

Example 42

1-(4-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-pyrrolidine-2-carboxylic acid **80** was synthesized according to the following procedure.

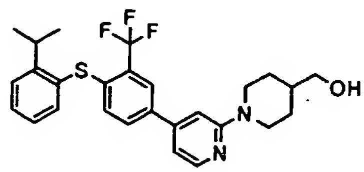


80

The title compound was prepared according to the procedures of Example 38E, substituting 3-hydroxypyrrolidine with (D)-proline. A yellow solid **80** was obtained (0.0232 g, 81%). ^1H NMR ($CDCl_3$, 400 MHz) δ 1.19 (d, J = 6.8 Hz, 6H), 2.13-2.34 (m, 4H), 2.47-2.53 (br, 1H), 3.50 (heptet, J = 6.8 Hz, 1H), 3.61 (br, 1H), 3.85 (br, 1H), 4.95 (br, 1H), 6.81 (s, 1H), 6.88-6.94 (m, 2H), 7.25-7.29 (m, 1H), 7.46-7.54 (m, 4H), 7.84 (s, 1H), 8.03 (d, J = 6.6 Hz, 1H). MS (APCI) m/z 487 $(M+H)^+$.

Example 43

(4'-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-3,4,5,6-tetrahydro-2*H*-(1,2')bipyridinyl-4-yl)-methanol **81** was synthesized according to the following procedure.

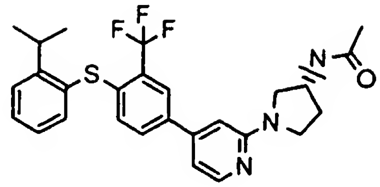


81

The title compound was prepared according to the procedures of Example 38E, substituting 3-hydroxypyrrolidine with 4-hydroxymethylpiperidine. A yellow solid **81** was obtained (0.0252 g, 88%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.19 (d, J = 6.8 Hz, 6H), 1.41-1.50 (m, 2H), 1.86-1.94 (m, 1H), 1.99 (d, J = 13.6 Hz, 2H), 3.27 (t, J = 11.7 Hz, 2H), 3.50 (heptet, J = 6.8 Hz, 1H), 3.57 (d, J = 5.8 Hz, 2H), 4.36 (d, J = 13.2 Hz, 2H), 6.85-6.94 (m, 2H), 6.97 (s, 1H), 7.25-7.29 (m, 1H), 7.46-7.54 (m, 4H), 7.84 (s, 1H), 8.22 (d, J = 6.6 Hz, 1H); MS (APCI) m/z 487 $(M+H)^+$.

Example 44

N-(1-(4-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-pyrrolidin-3-yl)-acetamide **82** was synthesized according to the following procedure.

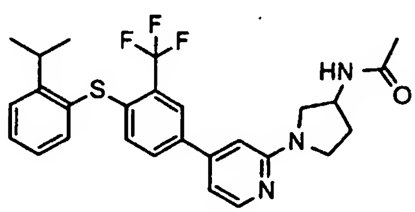


82

The title compound was prepared according to the procedures of Example 38E, substituting 3-hydroxypyrrolidine with (3R)-(+)-3-acetamidopyrrolidine. A yellow solid **82** was obtained (0.0243 g, 83%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.19 (d, J = 6.8 Hz, 6H), 1.97 (s, 3H), 2.22-2.28 (m, 1H), 2.31-2.37 (m, 1H), 3.50 (heptet, J = 6.8 Hz, 1H), 3.72-3.80 (m, 2H), 3.81-3.86 (m, 1H), 3.91-3.99 (m, 1H), 4.61-4.66 (m, 1H), 6.78 (s, 1H), 6.90 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 5.9 Hz, 1H), 7.25-7.29 (m, 1H), 7.46-7.54 (m, 4H), 7.86 (d, J = 1.5 Hz, 1H), 8.06 (d, J = 6.6 Hz, 1H); MS (APCI) m/z 500 $(M+H)^+$.

<u>Example 45</u>

N-(1-(4-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-pyrrolidin-3-yl)-acetamide **83** was synthesized according to the following procedure.



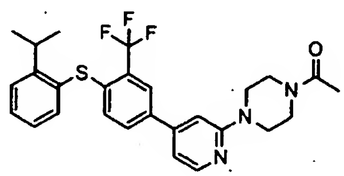
83

The title compound was prepared according to the procedures of Example 38E, substituting 3-hydroxypyrrolidine with 3-acetamidopyrrolidine. A yellow solid **83** was obtained (0.019 g, 65%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.19 (d, J = 6.8 Hz, 6H), 1.99 (s, 3H), 2.22-2.29 (m, 1H), 2.33-2.40 (m, 1H), 3.49 (heptet, J = 6.8 Hz, 1H), 3.73-3.81 (m,

2H), 3.82-3.87 (m, 1H), 3.96-4.04 (m, 1H), 4.62-4.67 (m, 1H), 6.78 (s, 1H), 6.90 (d, J = 8.4 Hz, 1H), 6.94 (d, J = 6.6 Hz, 1H), 7.26-7.29 (m, 1H), 7.46-7.54 (m, 4H), 7.85 (s, 1H), 8.03 (d, J = 6.6 Hz, 1H); MS (APCI) m/z 500 $(M+H)^+$.

Example 46

1-(4-(4-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-piperazin-1-yl)-ethanone **84** was synthesized according to the following procedure.

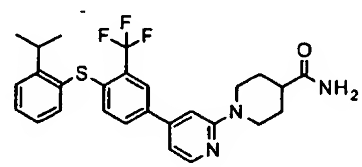


84

The title compound was prepared according to the procedures of Example 38E, substituting 3-hydroxypyrrolidine with 1-acetylpiperazine. A yellow solid **84** was obtained (0.0033 g, 11%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.19 (d, J = 6.8 Hz, 6H), 2.17 (s, 3H), 3.50 (heptet, J = 6.8 Hz, 1H), 3.68-3.72 (m, 2H), 3.73-3.77 (m, 2H), 3.83-3.89 (m, 2H), 3.96-4.00 (m, 2H), 6.91 (d, J = 8.4 Hz, 1H), 6.94 (s, 1H), 7.02 (d, J = 5.5 Hz, 1H), 7.25-7.29 (m, 1H), 7.46-7.54 (m, 4H), 7.86 (d, J = 1.4 Hz, 1H), 8.28 (d, J = 6.3 Hz, 1H); MS (APCI) m/z 500 $(M+H)^+$.

Example 47

4'-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-3,4,5,6-tetrahydro-2*H*-(1,2')bipyridinyl-4-carboxylic acid amide **85** was synthesized according to the following procedure.

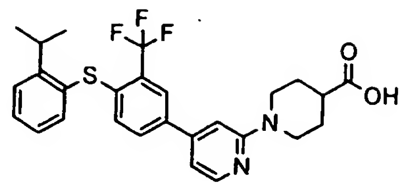


85

The title compound was prepared according to the procedures of Example 38E, substituting 3-hydroxypyrrolidine with isonipecotamide. A yellow solid **85** was obtained (0.0194 g, 66%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.19 (d, J = 6.8 Hz, 6H), 1.89-1.99 (m, 2H), 2.07-2.13 (m, 2H), 2.58-2.65 (m, 1H), 3.41 (t, J = 11.4 Hz, 2H), 3.50 (heptet, J = 6.8 Hz, 1H), 4.28 (d, J = 13.2 Hz, 2H), 5.65 (s, 1H), 6.06 (s, 1H), 6.90 (d, J = 8.4 Hz, 1H), 6.95 (d, J = 5.8 Hz, 1H), 6.99 (s, 1H), 7.25-7.29 (m, 1H), 7.44-7.52 (m, 4H), 7.85 (s, 1H), 8.18 (d, J = 6.6 Hz, 1H). MS (APCI) m/z 500 $(M+H)^+$.

Example 48

4'-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-3,4,5,6-tetrahydro-2*H*-(1,2')bipyridinyl-4-carboxylic acid **86** was synthesized according to the following procedure.

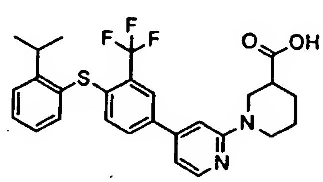


86

The title compound was prepared according to the procedures of Example 38E, substituting 3-hydroxypyrrolidine with isonipecotic acid. A yellow solid **86** was obtained (0.0112 g, 38%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.19 (d, J = 6.8 Hz, 6H), 1.90-1.99 (m, 2H), 2.09-2.16 (m, 2H), 2.70-2.77 (m, 1H), 3.43-3.53 (m, 3H), 4.11-4.17 (m, 2H), 6.90 (d, J = 8.4 Hz, 1H), 6.95 (d, J = 6.6 Hz, 1H), 6.99 (s, 1H), 7.25-7.29 (m, 1H), 7.46-7.54 (m, 4H), 7.84 (d, J = 1.1 Hz, 1H), 8.17 (d, J = 6.6 Hz, 1H); MS (APCI) m/z 501 $(M+H)^+$.

Example 49

4'-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-3,4,5,6-tetrahydro-2*H*-(1,2')bipyridinyl-3-carboxylic acid **87** was synthesized according to the following procedure.



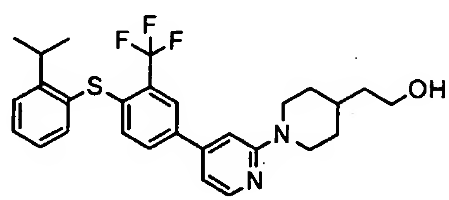
87

The title compound was prepared according to the procedures of Example 38E, substituting 3-hydroxypyrrolidine with nipecotic acid. A yellow solid **87** was obtained (0.0229 g, 78%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.19 (d, J = 6.8 Hz, 6H), 1.65-1.74 (m,

1H), 1.89-1.96 (m, 1H), 2.05-2.10 (m, 2H), 2.83-2.89 (m, 1H), 3.49 (heptet, J = 6.8 Hz, 1H), 3.56-3.63 (m, 1H), 3.78-3.88 (m, 2H), 4.13-4.18 (m, 1H), 6.91 (d, J = 8.4 Hz, 1H), 6.95 (d, J = 6.3 Hz, 1H), 7.07 (s, 1H), 7.25-7.29 (m, 1H), 7.46-7.54 (m, 4H), 7.85 (s, 1H), 8.26 (d, J = 6.6 Hz, 1H); MS (APCI) m/z 501 $(M+H)^+$.

Example 50

2-(4'-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-3,4,5,6-tetrahydro-2*H*-(1,2')bipyridinyl-4-yl-ethanol **88** was synthesized according to the following procedure.

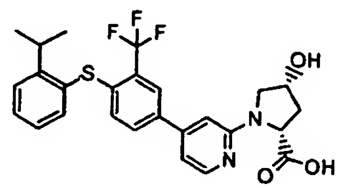


88

The title compound was prepared according to the procedures of Example 38E, substituting 3-hydroxypyrrolidine with 4-(1'-hydroxyethyl)piperidine. A yellow solid **88** was obtained (0.0245 g, 83%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.19 (d, J = 6.8 Hz, 6H), 1.34-1.44 (m, 1H),1.57 (q, J = 6.2 Hz, 2H), 1.84-1.93 (m, 1H), 1.97 (s, 1H), 2.00 (s, 1H), 3.25 (t, J = 12.5 Hz, 2H), 3.50 (heptet, J = 6.8 Hz, 1H), 3.74 (t, J = 6.4 Hz, 2H), 4.32 (s, 1H), 4.34 (s, 1H), 6.88-6.95 (m, 2H), 6.96 (s, 1H), 7.25-7.29 (m, 1H), 7.46-7.54 (m, 4H), 7.84 (s, 1H), 8.22 (d, J = 6.6 Hz, 1H); MS (APCI) m/z 501 $(M+H)^+$.

Example 51

4-Hydroxy-1-(4-(4-(2-isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-pyrrolidine-2-carboxylic acid **89** was synthesized according to the following procedure.

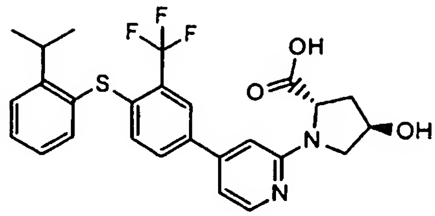


89

The title compound was prepared according to the procedures of Example 38E, substituting 3-hydroxypyrrolidine with cis-4-hydroxy-D-proline. A yellow solid **89** was obtained (0.0187 g, 63%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.19 (d, J = 6.8 Hz, 6H), 2.30-2.37 (m, 1H), 2.61 (d, J = 13.5 Hz, 1H), 3.49 (heptet, J = 6.8 Hz, 1H), 3.69-3.77 (m, 1H), 3.86-3.94 (m, 1H), 4.65 (s, 1H), 4.76-4.84 (m, 1H), 6.88 (d, J = 8.4 Hz, 2H), 6.96 (d, J = 6.3 Hz 1H), 7.25-7.29 (m, 1H), 7.46-7.54 (m, 4H), 7.83 (s, 1H), 7.99 (d, J = 6.6 Hz, 1H); MS (APCI) m/z 503 $(M+H)^+$.

Example 52

4-Hydroxy-1-(4-(4-(2-isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-pyrrolidine-2-carboxylic acid **90** was synthesized according to the following procedure.

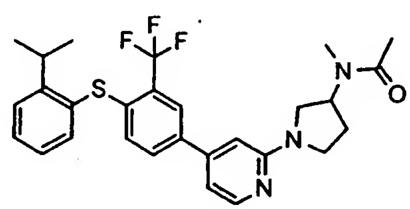


90

The title compound was prepared according to the procedures of Example 38E, substituting 3-hydroxypyrrolidine with trans-4-hydroxy-L-proline. A yellow solid **90** was obtained (0.0288 g, 97%). [1]H-NMR ($CDCl_3$, 400 MHz) δ 1.19 (d, J = 6.8 Hz, 6H), 2.44-2.50 (m, 1H), 2.65-2.67 (m, 1H), 3.49 (heptet, J = 6.8 Hz, 1H), 3.68-3.74 (m, 1H), 3.87-3.93 (m, 1H), 4.65-4.70 (m, 1H), 4.92-4.98 (m, 1H), 6.82 (s, 1H), 6.89 (d, J = 8.1 Hz, 1H), 6.94 (d, J = 1.7 Hz, 1H), 7.25-7.29 (m, 1H), 7.46-7.54 (m, 4H), 7.83 (s, 1H), 7.94-7.99 (br m, 1H). MS (APCI) m/z 503 $(M+H)^+$.

Example 53

N-1-(4-(4-(2-isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-pyrrolidine-3-yl)-N-methyl-acetamide **91** was synthesized according to the following procedure.

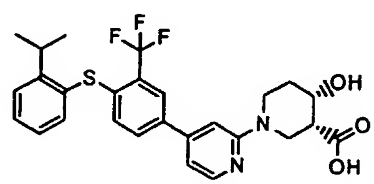


91

The title compound was prepared according to the procedures of Example 38E, substituting 3-hydroxypyrrolidine with 3-(*N*-acetyl-*N*-methylamino)pyrrolidine. A yellow solid **91** was obtained (0.0265 g, 88%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.19 (d, J = 6.8 Hz, 6H), 2.15 (s, 3H), 2.24-2.39 (m, 2H), 3.01 (s, 3H), 3.49 (heptet, J = 6.8 Hz, 1H), 3.63-3.78 (m, 2H), 3.91-4.06 (m, 2H), 5.18-5.26 (m, 1H), 6.76 (s, 1H), 6.90 (d, J = 8.4 Hz, 1H), 6.97 (d, J = 5.9 Hz, 1H), 7.25-7.29 (m, 1H), 7.46-7.54 (m, 4H), 7.86 (s, 1H), 8.18 (d, J = 6.3 Hz, 1H); MS (APCI) m/z 514 $(M+H)^+$.

Example 54

4-Hydroxy-4'-(4-(2-isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-3,4,5,6-tetrahydro-2*H*-(1,2')bipyridinyl-3-carboxylic acid **92** was synthesized according to the following procedure.



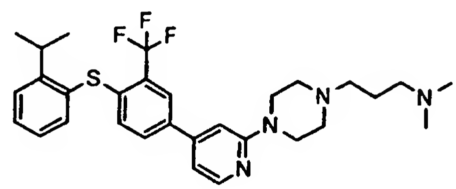
92

The title compound was prepared according to the procedures of Example 38E, substituting 3-hydroxypyrrolidine with (+/-)-cis-4-hydroxynipecotic acid. A yellow solid **92** was obtained (0.0087 g, 29%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.19 (d, J = 6.8 Hz, 6H), 1.73-1.82 (m, 1H), 2.02-2.08 (m, 1H), 2.96-3.01 (m, 1H), 3.49 (heptet, J = 6.8 Hz, 1H), 3.84 (d, J = 6.6 Hz, 2H), 4.00 (t, J = 12.6 Hz, 1H), 4.33 (d, J = 12.4 Hz, 1H), 4.46 (s,

1H), 6.91 (d, J = 8.4 Hz, 1H), 7.01 (d, J = 6.2 Hz 1H), 7.08 (s, 1H), 7.25-7.29 (m, 1H), 7.46-7.54 (m, 4H), 7.86 (s, 1H), 8.41 (d, J = 6.6 Hz, 1H); MS (APCI) m/z 517 $(M+H)^+$.

Example 55

(3-(4-(4-(4-(2-Isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-piperazin-1-yl)-propyl)-dimethyl-amine **93** was synthesized according to the following procedure.

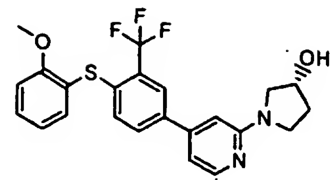


93

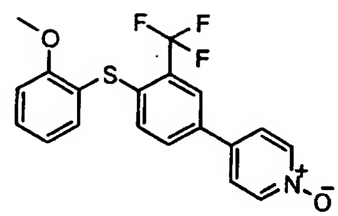
The title compound was prepared according to the procedures of Example 38E, substituting 3-hydroxypyrrolidine with 1-(3-dimethylaminopropyl)piperazine. A yellow solid **93** was obtained (0.027 g, 85%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.19 (d, J = 6.8 Hz, 6H), 2.43-2.50(m, 6H), 2.86 (s, 6H), 3.22-3.30 (m, 4H), 3.36-3.40 (m, 2H), 3.51 (heptet, J = 6.8 Hz, 1H), 4.08-4.12 (m, 2H), 6.83-6.94 (m, 2H), 7.01 (d, J = 5.5 Hz, 1H), 7.25-7.29 (m, 1H), 7.46-7.54 (m, 4H), 7.86 (s, 1H), 8.23 (d, J = 5.6 Hz, 1H); MS (APCI) m/z 543 $(M+H)^+$.

Example 56

1-(4-(4-(2-Methoxy-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-pyrrolidine-3-ol **94** was synthesized according to the following procedure.

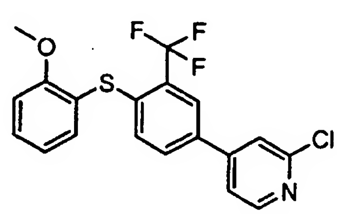


94



95

56A. First, 4-(4-(2-methoxy-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyridine 1-oxide **95** was prepared as follows. The title compound was prepared according to the procedures of Example 38C, substituting 2-isopropylthiophenol with 2-methoxythiophenol. A white solid **95** was obtained (1.02 g, 77%). ^{1}H-NMR (DMSO, 400 MHz) δ 3.79 (s, 3H), 7.04 (t, J = 1.1 Hz, 7.6 Hz, 1H), 7.08 (d, J = 8.0 Hz, 1H), 7.19 (dd, J = 0.8 Hz, 8.4 Hz, 1H), 7.33 (dd, J = 0.9 Hz, 8.4 Hz, 1H), 7.49 (dt, J = 1.7 Hz, 7.6 Hz, 1H), 7.84 (dt, J = 2.1Hz, 7.2 Hz, 2H), 7.91 (dd, J = 2.1 Hz, 8.4 Hz, 1H), 8.10 (d, J = 2.1 Hz, 1H), 8.26 (dt, J = 2.0 Hz, 7.2 Hz, 2H). MS (APCI) m/z 378 (M+H)$^+$.



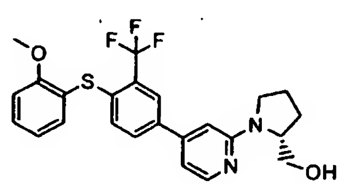
96

56B. Then 2-chloro-4-(4-(2-methoxy-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyridine **96** was prepared as follows. The title compound was prepared according to the procedures of Example 38D, substituting compound **75** with compound **95** (0.900g, 2.38 mmol). A yellow oil **96** was obtained (0.70 g, 74%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.83 (s, 3H), 6.98-7.03 (m, 2H), 7.09 (d, J = 8.2 Hz, 1H), 7.39(dd, J = 1.7 Hz, 5.1 Hz, 1H), 7.41-7.46 (m, 2H), 7.49-7.53 (m, 2H), 7.87 (d, J = 2.1 Hz, 1H), 8.43 (d, J = 4.7 Hz, 1H); MS (APCI m/z 396) $(M+H)^+$.

56C. The title compound was prepared according to the procedures of Example 38E, substituting compound **76** with compound **96** (0.039 g, 0.0985 mmol) and 3-hydroxypyrrolidine with (R)-3-hydroxypyrrolidine. A yellow solid **94** was obtained (0.0385 g, 87%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.13-2.31 (m, 2H), 3.83 (s, 3H), 3.88-3.95 (m, 4H), 4.74 (m, 1H), 6.79 (s, 1H), 6.92 (d, J = 6.6 Hz, 1H), 7.01-7.07 (m, 3H), 7.45-7.53 (m, 3H), 7.86 (s, 1H), 8.14 (d, J = 7.0 Hz, 1H); MS (APCI) m/z 447 $(M+H)^+$.

Example 57

1-(4-(4-(2-Methoxy-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-pyrrolidin-2-yl)-methanol **97** was synthesized according to the following procedure.

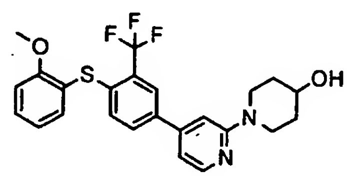


97

The title compound was prepared according to the procedures of Example 38E, substituting compound **76** with compound **96** (0.039 g, 0.0985 mmol) and 3-hydroxypyrrolidine with (R)-2-(hydroxymethyl)pyrrolidine. A yellow solid **97** was obtained (0.0233 g, 51%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.05-2.11 (m, 2H), 2.14-2.21 (m, 2H), 3.50 (q, J = 9.1 Hz, 1H), 3.62-3.76 (m, 3H), 3.83 (s, 3H), 4.59-4.65 (m, 1H), 6.79 (s, 1H), 6.92 (d, J = 6.3 Hz, 1H), 7.01-7.07 (m, 3H), 7.45-7.52 (m, 3H), 7.84 (s, 1H), 8.12 (d, J = 6.6 Hz, 1H). MS (APCI) m/z 461 $(M+H)^+$.

Example 58

4'-(4-(2-Methoxy-phenylsulfanyl)-3-trifluoromethyl-phenyl)-3,4,5,6-tetrahydro-2*H*-(1,2')bipyridinyl-4-ol **98** was synthesized according to the following procedure.

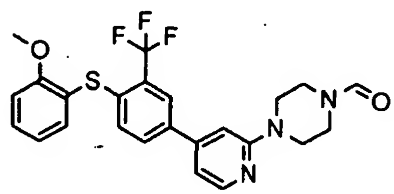


98

The title compound was prepared according to the procedures of Example 38E, substituting compound **76** with compound **96** (0.039g, 0.0985 mmol) and 3-hydroxypyrrolidine with 4-hydroxypiperidine. A yellow solid **98** was obtained (0.0299 g, 66%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.76-1.84 (m, 2H), 2.02-2.10 (m, 2H), 3.69-3.76 (m, 2H), 3.83 (s, 3H), 4.01-4.07 (m, 2H), 4.12-4.17 (m, 1H), 6.95 (d, J = 6.6 Hz, 1H), 6.99 (s, 1H), 7.01-7.07 (m, 3H), 7.46-7.52 (m, 3H), 7.85 (s, 1H), 8.23 (d, J = 6.6 Hz, 1H). MS (APCI) m/z 461 $(M+H)^+$.

Example 59

4-(4-(4-(2-Methoxy-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-piperazine-1-carbaldehyde **99** was synthesized according to the following procedure.

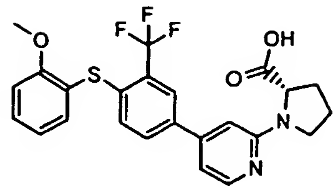


99

The title compound was prepared according to the procedures of Example 38E, substituting compound **76** with compound **96** (0.039g, 0.0985 mmol) and 3-hydroxypyrrolidine with 1-formylpiperazine. A yellow solid **99** was obtained (0.0159 g, 34%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.62-3.65 (m, 2H), 3.68-3.72 (m, 2H), 3.75-3.78 (m, 2H), 3.83 (s, 3H), 3.86-3.89 (m, 2H), 6.95 (s, 1H), 7.02 (m, 3H), 7.08 (d, J = 8.4 Hz, 1H), 7.46-7.52 (m, 3H), 7.86 (d, J = 1.5 Hz, 1H), 8.16 (s, 1H), 8.30 (d, J = 6.2 Hz, 1H); MS (APCI) m/z 474 $(M+H)^+$.

Example 60

1-(4-(4-(2-Methoxy-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-pyrrolidine-2-carboxylic acid **100** was synthesized according to the following procedure.

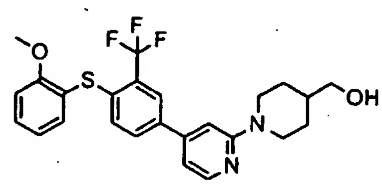


100

The title compound was prepared according to the procedures of Example 38E, substituting compound **76** with compound **96** (0.039g, 0.0985 mmol) and 3-hydroxypyrrolidine with (D)-proline. A yellow solid **100** was obtained (0.0366 g, 78%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.14-2.38 (m, 3H), 2.48-2.55 (m, 1H), 3.58-3.66 (m, 1H), 3.80-3.89 (m, 1H), 3.83 (s, 3H), 4.96-5.05 (m, 1H), 6.82 (s, 1H), 6.96 (d, J = 6.2 Hz, 1H), 7.01-7.07 (m, 3H), 7.46-7.52 (m, 3H), 7.84 (s, 1H), 8.04 (d, J = 6.2 Hz, 1H). MS (APCI) m/z 475 $(M+H)^+$.

<u>Example 61</u>

(4'-(4-(2-Methoxy-phenylsulfanyl)-3-trifluoromethyl-phenyl)-3,4,5,6-tetrahydro-2*H*-(1,2')bipyridinyl-4-yl)-methanol **101** was synthesized according to the following procedure.



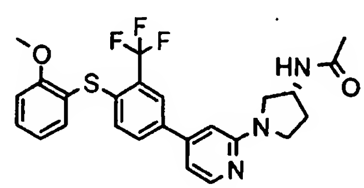
101

The title compound was prepared according to the procedures of Example 38E, substituting compound **76** with compound **96** (0.039 g, 0.0985 mmol) and 3-

hydroxypyrrolidine with 4-piperidinemethanol. A yellow solid **101** was obtained (0.0299 g, 64%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.41-1.50 (m, 2H), 1.86-1.94 (m, 1H), 1.97-2.03 (m, 2H), 3.27 (t, J = 13.6 Hz, 2H), 3.57 (d, J = 5.8 Hz, 2H), 3.83 (s, 3H), 4.38 (d, J = 13.5 Hz, 2H), 6.93 (d, J = 6.6 Hz, 1H), 6.97 (s, 1H), 7.01-7.07 (m, 3H), 7.46-7.52 (m, 3H), 7.84 (s, 1H), 8.24 (d, J = 6.2 Hz, 1H); MS (APCI) m/z 475 $(M+H)^+$.

Example 62

N-1-(4-(4-(2-Methoxy-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-pyrrolidine-3-yl)-acetamide **102** was synthesized according to the following procedure.

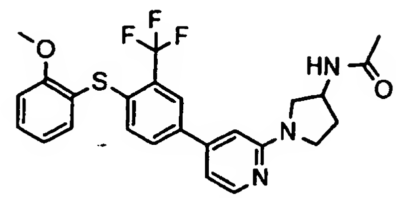


102

The title compound was prepared according to the procedures of Example 38E, substituting compound **76** with compound **96** (0.039 g, 0.0985 mmol) and 3-hydroxypyrrolidine with (3*R*)-(+)-3-acetamidopyrrolidine. A yellow solid **102** was obtained (0.0391 g, 81%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.00 (s, 3H), 2.23-2.29 (m, 1H), 2.33-2.40 (m, 1H), 3.78-3.88 (m, 3H), 3.83 (s, 3H), 4.00-4.07 (m, 1H), 4.62-4.67 (m, 1H), 6.78 (s, 1H), 6.95 (d, J = 6.6 Hz, 1H), 7.01-7.07 (m, 3H), 7.20 (br s, 1H), 7.46-7.52 (m, 3H), 7.85 (s, 1H), 8.06 (d, J = 6.6 Hz, 1H). MS (APCI) m/z 488 $(M+H)^+$.

Example 63

N-1-(4-(4-(2-Methoxy-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-pyrrolidine-3-yl)-acetamide **103** was synthesized according to the following procedure.

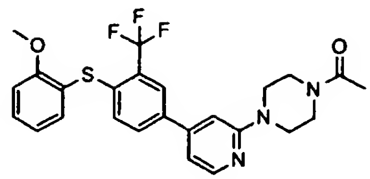


103

The title compound was prepared according to the procedures of Example 38E, substituting compound **76** with compound **96** (0.039g, 0.0985 mmol) and 3-hydroxypyrrolidine with 3-acetamidopyrrolidine. A yellow solid **103** was obtained (0.0306 g, 64%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.01 (s, 3H), 2.25-2.31 (m, 1H), 2.33-2.41 (m, 1H), 3.80-3.90 (m, 3H), 3.83 (s, 3H), 4.01-4.10 (m, 1H), 4.63-4.69 (m, 1H), 6.79 (s, 1H), 6.96 (d, J = 6.6 Hz, 1H), 7.01-7.07 (m, 3H), 7.12 (br s, 1H), 7.46-7.52 (m, 3H), 7.85 (s, 1H), 8.07 (d, J = 6.6 Hz, 1H). MS (APCI) m/z 488 $(M+H)^+$.

Example 64

1-(4-(4-(4-(2-Methoxy-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-piperazin-1-yl)-ethanone **104** was synthesized according to the following procedure.

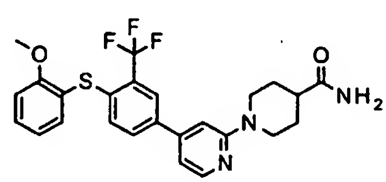


104

The title compound was prepared according to the procedures of Example 38E, substituting compound **76** with compound **96** (0.039g, 0.0985 mmol) and 3-hydroxypyrrolidine with 1-acetylpiperazine. A yellow solid **104** was obtained (0.0197 g, 41%).^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.17 (s, 3H), 3.68-3.72 (m, 2H), 3.73-3.78 (m, 2H), 3.82-3.89 (m, 2H), 3.83 (s, 3H), 3.94-3.99 (m, 2H), 6.95 (s, 1H), 7.00-7.05 (m, 3H), 7.07 (d, J = 8.4 Hz, 1H), 7.45-7.52 (m, 3H), 7.86 (s, 1H), 8.29 (d, J = 6.2 Hz, 1H). MS (APCI) m/z 488 $(M+H)^+$.

Example 65

(4'-(4-(2-Methoxy-phenylsulfanyl)-3-trifluoromethyl-phenyl)-3,4,5,6-tetrahydro-2*H*-(1,2')bipyridinyl-4-carboxylic acid amide **105** was synthesized according to the following procedure.



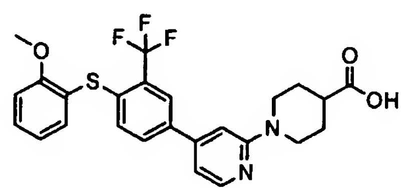
105

The title compound was prepared according to the procedures of Example 38E, substituting compound **76** with compound **96** (0.039 g, 0.0985 mmol) and 3-

hydroxypyrrolidine with isonipecotamide. A yellow solid **105** was obtained (0.0272 g, 57%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.90-1.99 (m, 2H), 2.08-2.14 (m, 2H), 2.59-2.66 (m, 1H), 3.39-3.47 (m, 2H), 3.83 (s, 3H), 4.29-4.34 (m, 2H), 5.57 (br s, 1H), 5.99 (br s, 1H), 6.97 (d, J = 6.6 Hz, 1H), 6.99 (s, 1H), 7.00-7.05 (m, 2H), 7.06 (d, J = 8.4 Hz, 1H), 7.46-7.52 (m, 3H), 7.85 (s, 1H), 8.20 (d, J = 6.6 Hz, 1H); MS (APCI) m/z 488 $(M+H)^+$.

Example 66

4'-(4-(2-Methoxy-phenylsulfanyl)-3-trifluoromethyl-phenyl)-3,4,5,6-tetrahydro-2*H*-(1,2')bipyridinyl-4-carboxylic acid **106** was synthesized according to the following procedure.

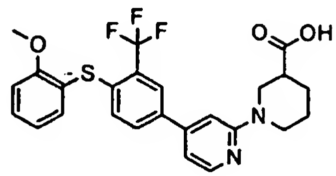


106

The title compound was prepared according to the procedures of Example 38E, substituting compound **76** with compound **96** (0.039 g, 0.0985 mmol) and 3-hydroxypyrrolidine with isonipecotic acid. A yellow solid **106** was obtained (0.0225 g, 47%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.90-1.99 (m, 2H), 2.09-2.16 (m, 2H), 2.68-2.77 (m, 1H), 3.43-3.50 (m, 2H), 3.83 (s, 3H), 4.14-4.20 (m, 2H), 6.95 (d, J = 6.2 Hz, 1H), 6.99-7.05 (m, 3H), 7.06 (d, J = 8.4 Hz, 1H), 7.45-7.52 (m, 3H), 7.84 (s, 1H), 8.20 (d, J = 6.6 Hz, 1H); MS (APCI) m/z 489 $(M+H)^+$.

Example 67

4'-(4-(2-Methoxy-phenylsulfanyl)-3-trifluoromethyl-phenyl)-3,4,5,6-tetrahydro-2*H*-(1,2')bipyridinyl-3-carboxylic acid amide **107** was synthesized according to the following procedure.

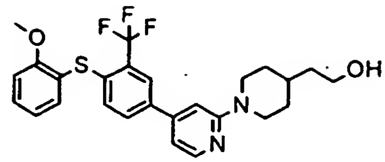


107

The title compound was prepared according to the procedures of Example 38E, substituting compound **76** with compound **96** (0.039 g, 0.0985 mmol) and 3-hydroxypyrrolidine with nipecotic acid. A yellow solid **107** was obtained (0.0283 g, 59%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.64-1.74 (m, 1H), 1.90-1.98 (m, 1H), 2.06-2.12 (m, 2H), 2.84-2.92 (m, 1H), 3.52-3.59 (m, 1H), 3.72-3.93 (m, 2H), 3.83 (s, 3H), 4.22-4.27 (m, 1H), 6.96 (d, J = 5.9 Hz, 1H), 7.00-7.08 (m, 4H), 7.45-7.52 (m, 3H), 7.84 (s, 1H), 8.31 (d, J = 6.5 Hz, 1H); MS (APCI) m/z 489 $(M+H)^+$.

Example 68

2-(4'-(4-(2-Methoxy-phenylsulfanyl)-3-trifluoromethyl-phenyl)-3,4,5,6-tetrahydro-2*H*-(1,2')bipyridinyl-4-yl)-ethanol **108** was synthesized according to the following procedure.

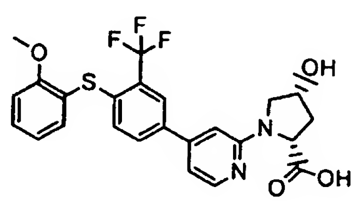


108

The title compound was prepared according to the procedures of Example 38E, substituting compound **76** with compound **96** (0.039g, 0.0985 mmol) and 3-hydroxypyrrolidine with 4-(2'-hydroxyethyl)piperidine. A yellow solid **108** was obtained (0.0308 g, 64%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.34-1.43 (m, 2H), 1.58 (q, J = 6.6 Hz, 2H), 1.84-1.93 (m, 1H), 1.96-2.02 (m, 2H), 3.21-3.29 (m, 2H), 3.74 (t, J = 6.2 Hz, 2H), 3.83 (s, 3H), 4.33-4.39 (m, 2H), 6.91 (d, J = 6.6 Hz, 1H), 6.96 (s, 1H), 7.00-7.07 (m, 3H), 7.45-7.52 (m, 3H), 7.84 (s, 1H), 8.24 (d, J = 6.6 Hz, 1H); MS (APCI) m/z 489 $(M+H)^+$.

Example 69

4-Hydroxy-1-(4-(4-(2-methoxy-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-pyrrolidine-2-carboxylic acid **109** was synthesized according to the following procedure.



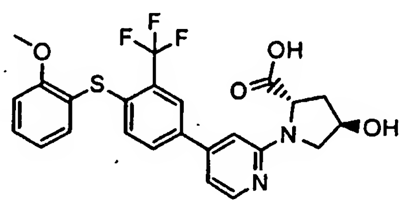
109

The title compound was prepared according to the procedures of Example 38E, substituting compound **76** with compound **96** (0.039 g, 0.0985 mmol) and 3-

hydroxypyrrolidine with cis-4-hydroxy-D-proline. A yellow solid **109** was obtained (0.030 g, 63%). MS (APCI) m/z 491 $(M+H)^+$.

Example 70

4-Hydroxy-1-(4-(4-(2-methoxy-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-pyrrolidine-2-carboxylic acid **110** was synthesized according to the following procedure.

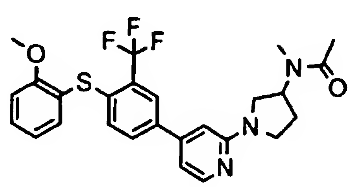


110

The title compound was prepared according to the procedures of Example 38E, substituting compound **76** with compound **96** (0.039 g, 0.0985 mmol) and 3-hydroxypyrrolidine with trans-4-hydroxy-L-proline. A yellow solid **110** was obtained (0.031 g, 65%). MS (APCI) m/z 491 $(M+H)^+$.

Example 71

N-1-(4-(4-(2-Methoxy-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-pyrrolidine-3-yl)-*N*-methyl-acetamide **111** was synthesized according to the following procedure.

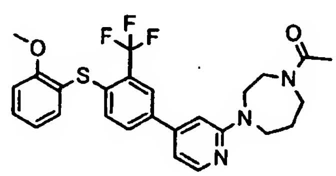


111

The title compound was prepared according to the procedures of Example 38E, substituting compound **76** with compound **96** (0.039 g, 0.0985 mmol) and 3-hydroxypyrrolidine with 3-(*N*-acetyl-*N*-methylamino)pyrrolidine. A yellow solid **111** was obtained (0.0211 g, 43%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.15 (s, 3H), 2.22-2.30 (m, 1H), 2.31-2.39 (m, 1H), 3.00 (s, 3H), 3.62-3.69 (m, 1H), 3.71-3.78 (m, 1H), 3.83 (s, 3H), 3.90-3.96 (m, 1H), 3.98-4.06 (m, 1H), 5.20-5.28 (m, 1H), 6.76 (s, 1H), 6.97 (d, J = 6.2 Hz, 1H), 7.00-7.04 (m, 2H), 7.06 (d, J = 8.4 Hz, 1H), 7.45-7.52 (m, 3H), 7.86 (s, 1H), 8.22 (d, J = 6.6 Hz, 1H); MS (APCI) m/z 502 $(M+H)^+$.

Example 72

1-(4-(4-(4-(2-Methoxy-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-(1,4)diazepan-1-yl)-ethanone **112** was synthesized according to the following procedure.



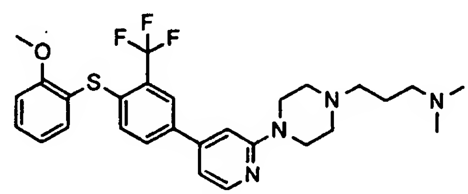
112

The title compound was prepared according to the procedures of Example 38E, substituting compound **76** with compound **96** (0.039 g, 0.0985 mmol) and 3-hydroxypyrrolidine with *N*-acetylhomopiperazine. A yellow solid **112** was obtained (0.0246 g, 50%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.02-2.10 (m, 2H), 2.08 (s, 3H), 3.55 (t, J = 5.9 Hz, 1H), 3.59 (t, J = 5.5 Hz, 1H), 3.79 (t, J = 6.2 Hz, 1H), 3.83 (s, 3H), 3.84-3.92

(m, 3H), 4.05 (t, J = 5.3 Hz, 1H), 4.15 (t, J = 5.5 Hz, 1H), 6.86 (s, 1/3H), 6.89 (s, 2/3H), 6.92-7.08 (m, 4H), 7.45-7.53 (m, 3H), 7.84 (s, 1/3H), 7.85 (s, 2/3H), 8.26-8.30 (m, 1H); MS (APCI) m/z 502 $(M+H)^+$.

Example 73

(3-(4-(4-(4-(2-Methoxy-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-piperazine-1-yl)-propyl)-dimethyl-amine **113** was synthesized according to the following procedure.

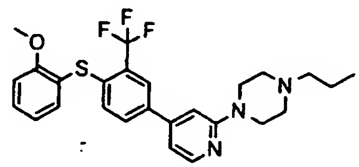


113

The title compound was prepared according to the procedures of Example 38E, substituting compound **76** with compound **96** (0.039 g, 0.0985 mmol) and 3-hydroxypyrrolidine with 1-(3-dimethylaminopropyl)piperazine. A yellow solid **113** was obtained (0.0414 g, 79%). ^1H NMR ($CDCl_3$, 400 MHz) δ 2.20-2.50 (br, 6H), 2.42-2.50 (m, 2H), 2.86 (s, 6H), 3.21-3.28 (m, 2H), 3.32-3.38 (br, 2H), 3.83 (s, 3H), 4.05-4.10 (br, 2H), 6.88 (s, 1H), 6.99-7.06 (m, 3H), 7.10 (d, J = 8.2 Hz, 1H), 7.43-7.52 (m, 3H), 7.85 (s, 1H), 8.25 (d, J = 5.5 Hz, 1H); MS (APCI) m/z 531 $(M+H)^+$.

Example 74

1-(4-(4-(2-Methoxy-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-4-propyl-piperazine **114** was synthesized according to the following procedure.

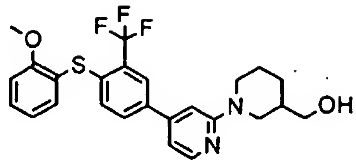


114

The title compound was prepared according to the procedures of Example 38E, substituting compound **76** with compound **96** (0.039 g, 0.0985 mmol) and 3-hydroxypyrrolidine with 1-propylpiperazine. A yellow solid **114** was obtained (0.033 g, 69%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.03 (t, J = 7.3Hz, 3H), 1.83-1.92 (m, 2H), 2.65-3.10 (br, 8H), 2.98-3.04 (m, 2H), 3.83 (s, 3H), 6.89 (s, 1H), 6.99-7.06 (m, 3H), 7.09 (d, J = 8.1 Hz, 1H), 7.43-7.52 (m, 3H), 7.85 (s, 1H), 8.26 (d, J = 5.9 Hz, 1H); MS (APCI) m/z 488 $(M+H)^+$.

Example 75

(4'-(4-(2-Methoxy-phenylsulfanyl)-3-trifluoromethyl-phenyl)-3,4,5,6-tetrahydro-2*H*-(1,2')bipyridinyl-3-yl)-methanol **115** was synthesized according to the following procedure.

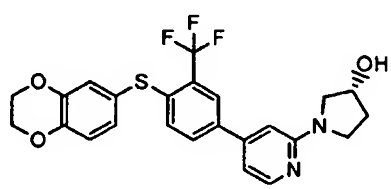


115

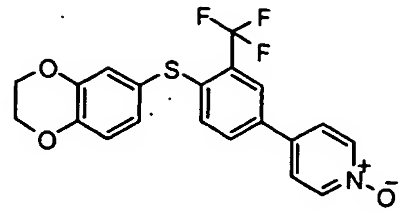
The title compound was prepared according to the procedures of Example 38E, substituting compound **76** with compound **96** (0.039 g, 0.0985 mmol) and 3-hydroxypyrrolidine with 3-hydroxymethyl piperidine. A yellow solid **115** was obtained (0.0279g, 60%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.32-1.42 (m, 1H), 1.63-1.74 (m, 1H), 1.86-1.95 (m, 2H), 2.04-2.14 (m, 1H), 3.18-3.25 (m, 1H), 3.33-3.39 (m, 1H), 3.47-3.52 (m, 1H), 3.71 (dd, J = 4.0 Hz, 11.0 Hz, 1H), 3.83 (s, 3H), 4.02-4.07 (m, 1H), 4.48-4.53 (m, 1H), 6.93 (d, J = 6.6 Hz, 1H), 7.00-7.08 (m, 4H), 7.45-7.52 (m, 3H), 7.84 (s, 1H), 8.35 (d, J = 6.5 Hz, 1H); MS (APCI) m/z 475 $(M+H)^+$.

Example 76

1-(4-(4-(2,3-Dihydro-benzo(1,4)dioxin-6-ylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-pyrrolidin-3-ol **116** was synthesized according to the following procedure.



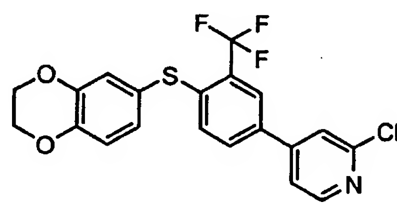
116



117

76A. First, 4-(4-(2,3-dihydro-benzo(1,4)dioxin-6-ylsulfanyl)-3-trifluoromethyl-phenyl)-pyridine 1-oxide **117** was synthesized according to the following procedure.

The title compound was prepared according to the procedures of Example 38C, substituting 2-isopropylthiophenol with 3,4-ethylenedioxythiophenol (0.671g, 3.99 mmol). A white solid **117** was obtained (1.39 g, 90%). ^{1}H-NMR (DMSO, 400 MHz) δ 4.27-4.34 (m, 4H), 7.01-7.08 (m, 3H), 7.12 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 7.3 Hz, 2H), 7.93 (dd, J = 2.2 Hz, 8.5 Hz, 1H), 8.09 (d, J = 2.2 Hz, 1H), 8.27 (d, J = 7.4 Hz, 2H); MS (APCI) m/z 406 $(M+H)^+$.



118

76B. Then, 2-chloro-(4-(4-(2,3-dihydro-benzo(1,4)dioxin-6-ylsulfanyl)-3-trifluoromethyl-phenyl)-pyridine **118** was synthesized according to the following procedure.

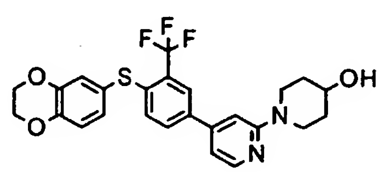
The title compound was prepared according to the procedures of Example 38D, substituting compound **75** with compound **117** (1.37 g, 3.38 mmol). A yellow oil **118** was obtained (0.87 g, 60%). ^{1}H-NMR (DMSO, 400 MHz) δ 4.28-4.35 (m, 4H), 7.03-7.13 (m, 4H), 7.80 (dd, J = 1.4 Hz, 5.2 Hz, 1H), 7.94 (d, J = 1.2 Hz, 1H), 7.99 (dd, J = 1.8

Hz, 8.5 Hz, 1H), 8.16 (d, J = 1.8 Hz, 1H), 8.47 (d, J = 5.2 Hz, 1H); MS (APCI) m/z 424 $(M+H)^+$.

76C. The title compound was prepared according to the procedures of Example 38E, substituting compound **76** with compound **118** (0.033 g, 0.0779 mmol) and 3-hydroxypyrrolidine with (R)-3-hydroxypyrrolidine. A yellow solid **116** was obtained (0.0353 g, 75%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.15-2.23 (m, 1H), 2.25-2.31 (m, 1H), 3.78-3.84 (m, 2H), 3.87-3.95 (m, 2H), 4.28-4.34 (m, 4H), 4.72-4.76 (m, 1H), 6.77 (s, 1H), 6.91 (dd, J = 1.1 Hz, 6.6 Hz, 1H), 6.95 (d, J = 8.1 Hz, 1H), 7.05 (dd, J = 2.1 Hz, 8.1 Hz, 1H), 7.10 (d, J = 2.2 Hz, 1H), 7.12 (d, J = 8.4 Hz, 1H), 7.54 (dd, J = 1.4 Hz, 8.5 Hz, 1H), 7.83 (d, J = 1.1 Hz, 1H), 8.15 (d, J = 6.6 Hz, 1H); MS (APCI) m/z 475 $(M+H)^+$.

Example 77

4'-(4-(2,3-Dihydro-benzo(1,4)dioxin-6-ylsulfanyl)-3-trifluoromethyl-phenyl)-3,4,5,6-tetrahydro-2*H*-(1,2')bipyridinyl-4-ol **119** was synthesized according to the following procedure.



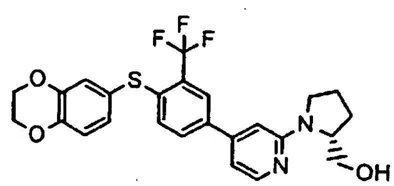
119

The title compound was prepared according to the procedures of Example 38E, substituting compound **76** with compound **118** (0.033 g, 0.0779 mmol) and 3-

hydroxypyrrolidine with 4-hydroxypiperidine. A yellow solid **119** was obtained (0.031 g, 63%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.75-1.84 (m, 2H), 2.02-2.10 (m, 2H), 3.67-3.74 (m, 2H), 4.00-4.07 (m, 2H), 4.10-4.16 (m, 1H), 4.28-4.34 (m, 4H), 4.72-4.76 (m, 1H), 6.93-6.97 (m, 3H), 7.05 (dd, J = 1.8 Hz, 8.0 Hz, 1H), 7.10 (d, J = 1.8 Hz, 1H), 7.12 (d, J = 8.5 Hz, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.82 (s, 1H), 8.25 (d, J = 6.3 Hz, 1H); MS (APCI) m/z 489 $(M+H)^+$.

Example 78

(1-(4-(4-(2,3-Dihydro-benzo(1,4)dioxin-6-ylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-pyrrolidin-2-yl)-methanol **120** was synthesized according to the following procedure.



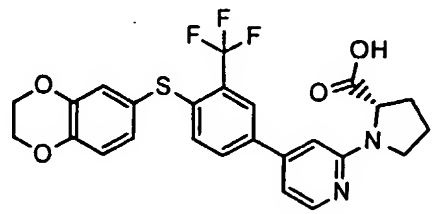
120

The title compound was prepared according to the procedures of Example 38E, substituting compound **76** with compound **118** (0.033 g, 0.0779 mmol) and 3-hydroxypyrrolidine with (*R*)-2-(hydroxymethyl)pyrrolidine. A yellow solid **120** was obtained (0.027 g, 55%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.06-2.11 (m, 2H), 2.16-.21 (m, 2H), 3.46-3.53 (m, 1H), 3.63-3.76 (m, 3H), 4.28-4.34 (m, 4H), 4.61-4.66 (m, 1H), 6.78 (s, 1H), 6.92 (dd, J = 1.4 Hz, 6.9 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 7.05 (dd, J = 2.2 Hz, 8.0

Hz, 1H), 7.10 (d, J = 2.2 Hz, 1H), 7.12 (d, J = 8.5 Hz, 1H), 7.52 (dd, J = 1.9 Hz, 8.4 Hz, 1H), 7.82 (d, J =1.4 Hz, 1H), 8.13 (d, J = 6.6 Hz, 1H); MS (APCI) m/z 489 $(M+H)^+$.

Example 79

1-(4-(4-(2,3-Dihydro-benzo(1;4)dioxin-6-ylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-pyrrolidine-2-carboxylic acid **121** was synthesized according to the following procedure.

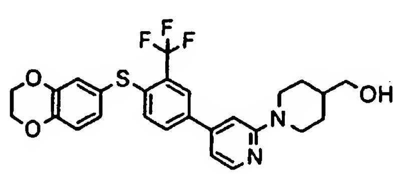


121

The title compound was prepared according to the procedures of Example 38E, substituting compound **76** with compound **118** (0.033 g, 0.0779 mmol) and 3-hydroxypyrrolidine with (D)-proline. A yellow solid **121** was obtained (0.035 g, 70%). MS (APCI) m/z 503 $(M+H)^+$.

Example 80

(4'-(4-(2,3-Dihydro-benzo(1,4)dioxin-6-ylsulfanyl)-3-trifluoromethyl-phenyl)-3,4,5,6-tetrahydro-2*H*-(1,2')bipyridinyl-4-yl)-methanol **122** was synthesized according to the following procedure.

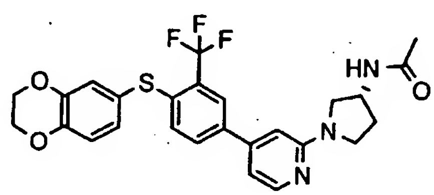


122

The title compound was prepared according to the procedures of Example 38E, substituting compound **76** with compound **118** (0.033 g, 0.0779 mmol) and 3-hydroxypyrrolidine with 4-piperidinemethanol. A yellow solid **122** was obtained (0.0284 g, 57%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.41-1.51 (m, 2H), 1.86-1.95 (m, 1H), 1.97-2.04 (m, 2H), 3.23-3.31 (m, 2H), 3.57 (d, J = 5.8 Hz, 2H), 4.28-4.34 (m, 4H), 4.36-4.41 (m, 2H), 6.92 (d, J = 6.6 Hz, 1H), 6.93-6.97 (m, 2H), 7.05 (dd, J = 1.8 Hz, 8.4 Hz, 1H), 7.09 (d, J = 1.8 Hz, 1H), 7.12 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.82 (s, 1H), 8.25 (d, J = 6.6 Hz, 1H); MS (APCI) m/z 503 $(M+H)^+$.

Example 81

N-(1-(4-(4-(2,3-Dihydro-benzo(1,4)dioxin-6-ylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-pyrrolidin-3-yl)-acetamide **123** was synthesized according to the following procedure.



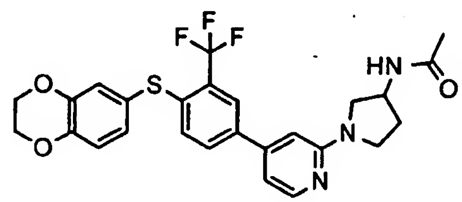
123

The title compound was prepared according to the procedures of Example 38E, substituting compound **76** with compound **118** (0.033 g, 0.0779 mmol) and 3-hydroxypyrrolidine with (3*R*)-(+)-3-acetamidopyrrolidine. A yellow solid **123** was obtained (0.0397 g, 78%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.03 (s, 3H), 2.25-2.31 (m, 1H), 2.34-2.42 (m, 1H), 3.80-3.90 (m, 3H), 4.02-4.11 (m, 1H), 4.28-4.34 (m, 4H), 4.63-

4.68 (m, 1H), 6.78 (s, 1H), 6.93-6.97 (m, 2H), 7.05 (dd, J = 2.2 Hz, 8.4 Hz, 1H), 7.09-7.13 (m, 2H), 7.18 (brs, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.83 (s, 1H), 8.07 (d, J = 6.6 Hz, 1H); MS (APCI) m/z 516 $(M+H)^+$.

Example 82

N-(1-(4-(4-(2,3-Dihydro-benzo(1,4)dioxin-6-ylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-pyrrolidin-3-yl)-acetamide **124** was synthesized according to the following procedure.

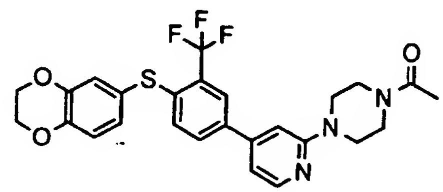


124

The title compound was prepared according to the procedures of Example 38E, substituting compound **76** with compound **118** (0.033g, 0.0779 mmol) and 3-hydroxypyrrolidine with 3-acetamidopyrrolidine. A yellow solid **124** was obtained (0.0369 g, 72%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.01 (s, 3H), 2.24-2.31 (m, 1H), 2.34-2.41 (m, 1H), 3.78-3.90 (m, 3H), 4.01-4.10 (m, 1H), 4.28-4.34 (m, 4H), 4.62-4.68 (m, 1H), 6.78 (s, 1H), 6.93-6.97 (m, 2H), 7.05 (dd, J = 2.2 Hz, 8.4 Hz, 1H), 7.09-7.13 (m, 2H), 7.18 (br s, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.83 (s, 1H), 8.07 (d, J = 6.6 Hz, 1H); MS (APCI) m/z 516 $(M+H)^+$.

Example 83

(1-(4-(4-(4-(2,3-Dihydro-benzo(1,4)dioxin-6-ylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-piperazin-1-yl)-ethanone **125** was synthesized according to the following procedure.

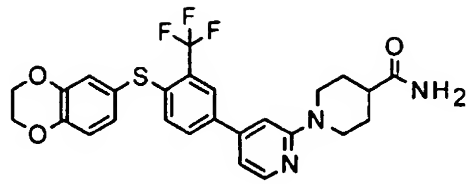


125

The title compound was prepared according to the procedures of Example 38E, substituting compound **76** with compound **118** (0.033 g, 0.0779 mmol) and 3-hydroxypyrrolidine with 1-acetylpiperazine. A yellow solid **125** was obtained (0.010 g, 19%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.17 (s, 3H), 3.67-3.72 (m, 2H), 3.73-3.77 (m, 2H), 3.83-3.88 (m, 2H), 3.94-3.98 (m, 2H), 4.28-4.34 (m, 4H), 6.93 (s, 1H), 6.95 (d, J = 8.4 Hz, 1H), 7.02 (d, J = 5.8 Hz, 1H), 7.05 (dd, J = 2.2 Hz, 8.4 Hz, 1H), 7.09 (d, J = 2.2 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 7.53 (d, J = 8.1 Hz, 1H), 7.83 (s, 1H), 8.29 (d, J = 6.2 Hz, 1H); MS (APCI) m/z 516 $(M+H)^+$.

Example 84

4'-(4-(2,3-Dihydro-benzo(1,4)dioxin-6-ylsulfanyl)-3-trifluoromethyl-phenyl)-3,4,5,6-tetrahydro-2*H*-(1,2')bipyridinyl-4-carboxylic acid amide **126** was synthesized according to the following procedure.

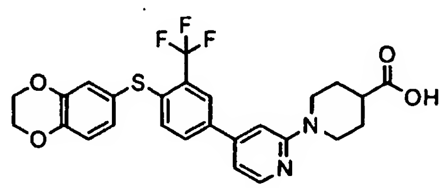


126

The title compound was prepared according to the procedures of Example 38E, substituting compound **76** with compound **118** (0.033 g, 0.0779 mmol) and 3-hydroxypyrrolidine with isonipecotamide. A yellow solid **126** was obtained (0.024 g, 47%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.90-1.99 (m, 2H), 2.08-2.14 (m, 2H), 2.58-2.65 (m, 1H), 3.38-3.45 (m, 2H), 4.28-4.34 (m, 6H), 5.55 (br s, 1H), 5.97 (br s, 1H), 6.93-6.98 (m, 3H), 7.05 (dd, J = 2.0 Hz, 8.2 Hz, 1H), 7.09 (d, J = 1.8 Hz, 1H), 7.12 (d, J = 8.4 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.82 (s, 1H), 8.21 (d, J = 6.6 Hz, 1H); MS (APCI) m/z 516 $(M+H)^+$.

Example 85

4'-(4-(2,3-Dihydro-benzo(1,4)dioxin-6-ylsulfanyl)-3-trifluoromethyl-phenyl)-3,4,5,6-tetrahydro-2*H*-(1,2')bipyridinyl-4-carboxylic acid **127** was synthesized according to the following procedure.



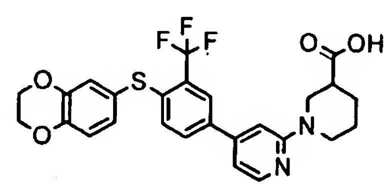
127

The title compound was prepared according to the procedures of Example 38E, substituting compound **76** with compound **118** (0.033 g, 0.0779 mmol) and 3-

hydroxypyrrolidine with isonipecotic acid. A yellow solid **127** was obtained (0.014 g, 28%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.89-1.98 (m, 2H), 2.08-2.15 (m, 2H), 2.68-2.76 (m, 1H), 3.40-3.48 (m, 2H), 4.13-4.20 (m, 2H), 4.28-4.34 (m, 4H), 6.91-6.98 (m, 3H), 7.04 (dd, J = 1.9 Hz, 8.4 Hz, 1H), 7.09 (d, J = 2.2 Hz, 1H), 7.12 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.82 (s, 1H), 8.20 (d, J = 6.2 Hz, 1H); MS (APCI) m/z 517 $(M+H)^+$.

Example 86

4'-(4-(2,3-Dihydro-benzo(1,4)dioxin-6-ylsulfanyl)-3-trifluoromethyl-phenyl)-3,4,5,6-tetrahydro-2*H*-(1,2')bipyridinyl-3-carboxylic acid **128** was synthesized according to the following procedure.

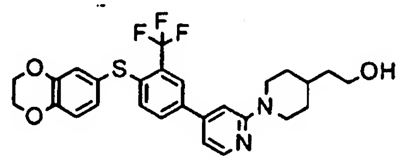


128

The title compound was prepared according to the procedures of Example 38E, substituting compound **76** with compound **118** (0.033 g, 0.0779 mmol) and 3-hydroxypyrrolidine with nipecotic acid. A yellow solid **128** was obtained (0.034 g, 66%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.64-1.74 (m, 1H), 1.92-1.99 (m, 1H), 2.06-2.13 (m, 2H), 2.88-2.95 (m, 1H), 3.50-3.57 (m, 1H), 3.68-3.74 (m, 2H), 3.90-3.96 (m, 1H), 4.28-4.36 (m, 4H), 6.94-6.98 (m, 2H), 7.03-7.07 (m, 2H), 7.09 (d, J = 1.9 Hz, 1H), 7.12 (d, J = 8.8 Hz, 1H), 7.52 (d, J = 8.5 Hz, 1H), 7.82 (s, 1H), 8.32 (d, J = 6.2 Hz, 1H); MS (APCI) m/z 517 $(M+H)^+$.

Example 87

2-(4'-(4-(2,3-Dihydro-benzo(1,4)dioxin-6-ylsulfanyl)-3-trifluoromethyl-phenyl)-3,4,5,6-tetrahydro-2*H*-(1,2')bipyridinyl-4-yl)-ethanol **129** was synthesized according to the following procedure.

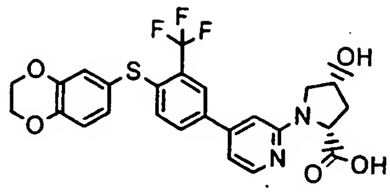


129

The title compound was prepared according to the procedures of Example 38E, substituting compound **76** with compound **118** (0.033 g, 0.0779 mmol) and 3-hydroxypyrrolidine with 4-(2'-hydroxyethyl)piperidine. A yellow solid **129** was obtained (0.037 g, 73%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.35-1.44 (m, 2H), 1.55-1.60 (m, 2H), 1.84-1.93 (m, 1H), 1.97-2.03 (m, 2H), 3.22-3.30 (m, 2H), 3.74 (t, J = 6.2 Hz, 2H), 4.28-4.34 (m, 4H), 4.36-4.42 (m, 2H), 6.91 (d, J = 6.6 Hz, 1H), 6.93-6.96 (m, 2H), 7.05 (dd, J = 2.2 Hz, 8.4 Hz, 1H), 7.09 (d, J = 2.2 Hz, 1H), 7.12 (d, J = 8.8 Hz, 1H), 7.51 (d, J = 8.8 Hz, 1H), 7.81 (s, 1H), 8.24 (d, J = 6.6 Hz, 1H); MS (APCI) m/z 517 $(M+H)^+$.

Example 88

1-(4-(4-(2,3-Dihydro-benzo(1,4)dioxin-6-ylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-4-hydroxy-pyrrolidine-2-carboxylic acid **130** was synthesized according to the following procedure.

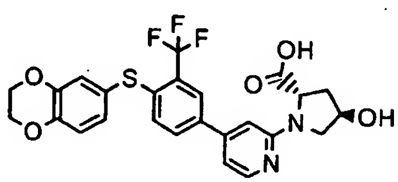


130

The title compound was prepared according to the procedures of Example 38E, substituting compound **76** with compound **118** (0.033 g, 0.0779 mmol) and 3-hydroxypyrrolidine with *cis*-4-hydroxy-D-proline. A yellow solid **130** was obtained (0.038 g, 74%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.34-2.42 (m, 1H), 2.64-2.68 (m, 2H), 3.73-3.82 (m, 1H), 3.94-4.00 (m, 1H), 4.28-4.34 (m, 4H), 4.68-4.74 (m, 1H), 6.92-7.12 (m, 6H), 7.52 (br, 1H), 7.80 (s, 1H), 8.04 (br, 1H); MS (APCI) m/z 519 $(M+H)^+$.

<u>Example 89</u>

1-(4-(4-(2,3-Dihydro-benzo(1,4)dioxin-6-ylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-4-hydroxy-pyrrolidine-2-carboxylic acid **131** was synthesized according to the following procedure.



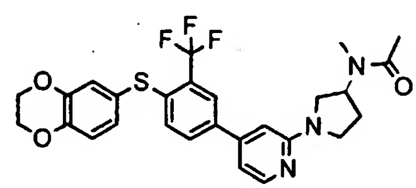
131

The title compound was prepared according to the procedures of Example 38E, substituting compound **76** with compound **118** (0.033 g, 0.0779 mmol) and 3-

hydroxypyrrolidine with trans-4-hydroxy-L-proline. A yellow solid **131** was obtained (0.017 g, 33%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.42-2.51 (m, 1H), 3.66-3.72 (m, 1H), 3.85-3.91 (m, 1H), 4.00-4.06 (m, 1H), 4.28-4.34 (m, 4H), 4.64-4.69 (m, 1H), 4.89-4.95 (m, 1H), 6.81 (s, 1H), 6.92-6.96 (m, 2H), 7.03 (dd, J = 1.8 Hz, 8.4 Hz, 1H), 7.06-7.10 (m, 2H), 7.50 (d, J = 8.4 Hz, 1H), 7.79 (s, 1H), 7.92-7.96 (m, 1H); MS (APCI) m/z 519 $(M+H)^+$.

Example 90

N-1-(4-(4-(2,3-Dihydro-benzo(1,4)dioxin-6-ylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-pyrrolidin-3-yl)-*N*-methyl-acetamide **132** was synthesized according to the following procedure.



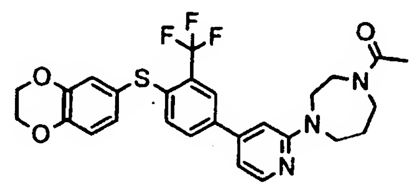
132

The title compound was prepared according to the procedures of Example 38E, substituting compound **76** with compound **118** (0.033 g, 0.0779 mmol) and 3-hydroxypyrrolidine with 3-(*N*-acetyl-*N*-methylamino)pyrrolidine. A yellow solid **132** was obtained (0.022 g, 42%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.15 (s, 3H), 2.20-2.29 (m, 1H), 2.32-2.40 (m, 1H), 3.00 (s, 3H), 3.62-3.70 (m, 1H), 3.71-3.78 (m, 1H), 3.90-3.96 (m, 1H), 3.98-4.06 (m, 1H), 4.28-4.34 (m, 4H), 5.21-5.29 (m, 1H), 6.74 (s, 1H), 6.93-6.97 (m, 2H),

7.05 (dd, J = 2.2 Hz, 8.4 Hz, 1H), 7.10 (d, J = 1.8 Hz, 1H), 7.12 (d, J = 8.4 Hz, 1H), 7.53 (d, J = 8.1 Hz, 1H), 7.83 (s, 1H), 8.23 (d, J = 6.6 Hz, 1H); MS (APCI) m/z 530 $(M+H)^+$.

Example 91

1-(4-(4-(4-(2,3-Dihydro-benzo(1,4)dioxin-6-ylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-(1,4)diazepan-1-yl)-ethanone **133** was synthesized according to the following procedure.

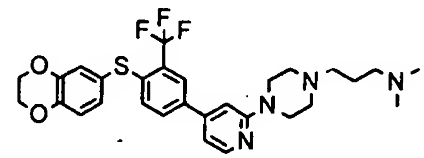


133

The title compound was prepared according to the procedures of Example 38E, substituting compound **76** with compound **118** (0.033 g, 0.0779 mmol) and 3-hydroxypyrrolidine with *N*-acetylhomopiperazine. A yellow solid **133** was obtained (0.021 g, 40%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.01-2.10 (m, 2H), 2.08 (s, 3H), 3.52-3.60 (m, 2H), 3.76-3.91 (m, 4H), 4.01-4.06 (m, 1H), 4.11-4.16 (m, 1H), 4.28-4.34 (m, 4H), 6.85 (s, 1/3H), 6.87 (s, 2/3H), 6.95 (d, J = 8.4 Hz, 1H), 6.97 (d, J = 6.6 Hz, 1H), 7.05 (dd, J = 1.4 Hz, 8.4 Hz, 1H), 7.10 (d, J = 2.2 Hz, 1H), 7.11-7.14 (m, 1H), 7.50-7.56 (m, 1H), 7.81 (s, 1/3H), 7.82 (s, 2/3H), 8.26-8.30 (m, 1H);MS (APCI) m/z 530 $(M+H)^+$.

Example 92

(3-(4-(4-(4-(2,3-Dihydro-benzo(1,4)dioxin-6-ylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-piperazin-1-yl)-propyl)-dimethyl-amine **134** was synthesized according to the following procedure.

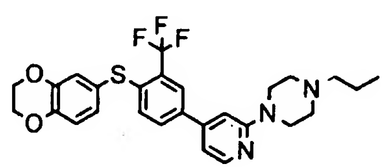


134

The title compound was prepared according to the procedures of Example 38E, substituting compound **76** with compound **118** (0.033 g, 0.0779 mmol) and 3-hydroxypyrrolidine with 1-(3-dimethylaminopropyl)piperazine. A yellow solid **134** was obtained (0.0401g, 73%). MS (APCI) m/z 559 $(M+H)^+$.

Example 93

1-(4-(4-(2,3-Dihydro-benzo(1,4)dioxin-6-ylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-4-propyl-piperazine **135** was synthesized according to the following procedure.



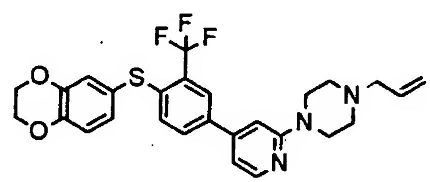
135

The title compound was prepared according to the procedures of Example 38E, substituting compound **76** with compound **118** (0.033 g, 0.0779 mmol) and 3-

hydroxypyrrolidine with 1-propylpiperazine. A yellow solid **135** was obtained (0.033 g, 64%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.03 (t, J = 7.3 Hz, 3H), 1.84-1.92 (m, 2H), 2.30-2.52 (br, 8H), 2.98-3.03 (m, 2H), 4.28-4.34 (m, 4H), 6.87 (s, 1H), 6.94 (d, J = 8.1 Hz, 1H), 7.01 (d, J= 5.8 Hz, 1H), 7.04 (dd, J = 2.2 Hz, 8.4 Hz, 1H), 7.09 (d, J = 2.2 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 7.51 (d, J = 8.3 Hz, 1H), 7.82 (s, 1H), 8.26 (d, J = 5.9 Hz, 1H); MS (APCI) m/z 516 $(M+H)^+$.

Example 94

1-Allyl-4-(4-(4-(2,3-dihydro-benzo(1,4)dioxin-6-ylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-piperazine **136** was synthesized according to the following procedure.



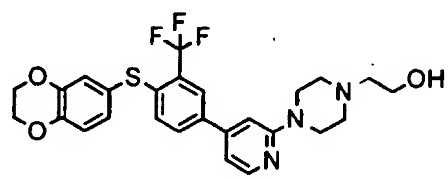
136

The title compound was prepared according to the procedures of Example 38E, substituting compound **76** with compound **118** (0.033g, 0.0779 mmol) and 3-hydroxypyrrolidine with 1-allylpiperazine. A yellow solid **136** was obtained (0.037 g, 73%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.10-2.55 (br m, 6H), 3.24-3.45 (br m, 2H), 3.7 (d, J = 7.0 Hz, 2H), 4.06-4.20 (br, 2H), 4.28-4.34 (m, 4H), 5.54 (d, J = 7.2 Hz, 1H), 5.61 (d, J = 10.2 Hz, 1H), 6.06 (m, 1H), 6.88 (s, 1H), 6.94 (d, J = 8.4 Hz, 1H), 7.02-7.06 (m, 2H),

7.09 (d, J = 1.9 Hz, 1H), 7.13 (d, J = 8.1 Hz, 1H), 7.52 (d, J = 8.1 Hz, 1H), 7.82 (s, 1H), 8.26 (d, J = 5.9 Hz, 1H); MS (APCI) m/z 514 $(M+H)^+$.

Example 95

2-(4-(4-(4-(2,3-Dihydro-benzo(1,4)dioxin-6-ylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-piperazin-1-yl)-ethanol **137** was synthesized according to the following procedure.

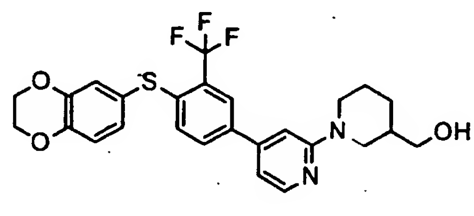


137

The title compound was prepared according to the procedures of Example 38E, substituting compound **76** with compound **118** (0.033 g, 0.0779 mmol) and 3-hydroxypyrrolidine with 1-(2'-hydroxyethyl)piperazine. A yellow solid **137** was obtained (0.034 g, 67%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.65-3.20 (br m, 4H), 3.24 (br m, 2H), 3.42-3.54 (m, 2H), 4.06 (br m, 2H), 4.05-4.18 (br m, 2H), 4.28-4.34 (m, 4H), 6.88 (s, 1H), 6.94 (d, J = 8.4 Hz, 1H), 7.02-7.06 (m, 2H), 7.09 (d, J = 2.2 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 7.7 Hz, 1H), 7.82 (s, 1H), 8.25 (d, J = 5.9 Hz, 1H); MS (APCI) m/z 518 $(M+H)^+$.

Example 96

(4'-(4-(2,3-Dihydro-benzo(1,4)dioxin-6-ylsulfanyl)-3-trifluoromethyl-phenyl)-3,4,5,6-tetrahydro-2*H*-(1,2')bipyridnyl-3-yl)-methanol **138** was synthesized according to the following procedure.



138

The title compound was prepared according to the procedures of Example 38E, substituting compound **76** with compound **118** (0.033 g, 0.0779 mmol) and 3-hydroxypyrrolidine with 3-hydryoxymethylpiperidine. A yellow solid **138** was obtained (0.030 g, 60%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.33-1.42 (m, 1H), 1.65-1.74 (m, 1H), 1.87-1.94 (m, 2H), 2.06-2.14 (m, 1H), 3.20-3.26 (m, 1H), 3.33-3.40 (m, 1H), 3.47-3.53 (m, 1H), 3.70-3.75 (m, 1H), 4.02-4.08 (m, 1H), 4.28-4.34 (m, 4H), 4.50-4.56 (m, 1H), 6.92 (d, J = 6.6 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 7.01 (s, 1H), 7.05 (dd, J = 2.2 Hz, 8.4 Hz, 1H), 7.09 (d, J = 1.8 Hz, 1H), 7.12 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 8.3 Hz, 1H), 7.83 (s, 1H), 8.33 (d, J = 6.6 Hz, 1H); MS (APCI) m/z 503 $(M+H)^+$.

Example 97

Compounds that antagonize the interaction between ICAM-1 and LFA-1 can be identified, and their activities quantitated, using both biochemical and cell-based adhesion assays. A primary biochemical assay, described below as assay 97A, was utilized to

measure the ability of the present compounds to block the interaction between the integrin LFA-1 and its adhesion partner ICAM-1.

97A. ICAM-1 / LFA-1 Biochemical Interaction Assay

In the biochemical assay, 100 mL of anti-LFA-1 antibody (ICOS Corporation) at a concentration of 5 mg/ml in Dulbecco's phosphate-buffered saline (D-PBS) is used to coat wells of a 96-well microtiter plate overnight at 4°C. The wells are then washed twice with wash buffer (D-PBS w/o Ca^{++} or Mg^{++}, 0.05% Tween 20) and blocked by addition of 200 mL of D-PBS, 5% fish skin gelatin. Recombinant LFA-1 (100 mL of 0.7 mg/ml, ICOS Corporation) in D-PBS is then added to each well. Incubation continues for 1 hour at room temperature and the wells are washed twice with wash buffer. Serial dilutions of compounds being assayed as ICAM-1/LFA-1 antagonists, prepared as 10 mM stock solutions in dimethyl sulfoxide (DMSO), are diluted in D-PBS, 2mM $MgCl_2$, 1% fish skin gelatin and 50 mL of each dilution added to duplicate wells. This is followed by addition of 50 mL of 0.8 mg/ml biotinylated recombinant ICAM-1/Ig (ICOS Corporation) to the wells and the plates are incubated at room temperature for 1 hour. The wells are then washed twice with wash buffer and 100 mL of Europium-labeled Streptavidin (Wallac Oy) diluted 1:100 in Delfia assay buffer (Wallac Oy) are added to the wells. Incubation proceeds for 1 hour at room temperature. The wells are washed eight times with wash buffer and 100 μL of enhancement solution (Wallac Oy, cat. No. 1244-105) are added to each well. Incubation proceeds for 5 minutes with constant mixing. Time-resolved fluorimetry measurements are made using the Victor 1420 Multilabel Counter (Wallac Oy) and the percent inhibition of each candidate compound is calculated using the following equation:

$$\% \text{ inhibition} = 100 \text{ X} \left\{ 1 - \frac{\text{average OD w/ compound minus background}}{\text{average OD w/o compound minus background}} \right\}$$

where "background" refers to wells that are not coated with anti-LFA-1 antibody.

The compounds inhibit the binding of ICAM-1 to LFA-1 with an IC_{50} less than 20 micromolar.

Biologically relevant activity of the compounds in this invention was confirmed using a cell-based adhesion assay, (described below as assay 97B) which measured the ability of the present compounds to block the adherence of JY-8 cells (a human EBV-transformed B cell line expressing LFA-1 on its surface) to immobilized ICAM-1.

97B. ICAM-1 / JY-8 cell adhesion assay

For measurement of inhibitory activity in the cell-based adhesion assay, 96-well microtiter plates are coated with 70 µL of recombinant ICAM-1/Ig (ICOS Corporation) at a concentration of 5 µg/mL in D-PBS w/o Ca^{++} or Mg^{++} overnight at 4°C. The wells are then washed twice with D-PBS and blocked by addition of 200 µL of D-PBS, 5% fish skin gelatin by incubation for 1 hour at room temperature. Fluorescent tagged JY-8 cells (a human EBV-transformed B cell line expressing LFA-1 on its surface; 50 µL at 2 x 10^6 cells/ml in RPMI 1640 (standard cell culture medium) /1% fetal bovine serum) are added to the wells. For fluorescent labeling of JY-8 cells, 5 x 10^6 cells washed once in RPMI 1640 are resuspended in 1 mL of RPMI 1640 containing 2 µM Calceiun AM (MolecularProbes), are incubated at 37°C for 30 minutes and washed once with RPMI-1640/ 1% fetal bovine serum. Dilutions of compounds to be assayed for ICAM-1/LFA-1 antagonistic activity are prepared in RPMI-1640/ 1% fetal bovine serum from 10mM stock solutions in DMSO and 50 µL are added to duplicate wells. Microtiter plates are

incubated for 45 minutes at room temperature and the wells are washed gently once with RPMI-1640/ 1% fetal bovine serum. Fluorescent intensity is measured in a fluorescent plate reader with an excitation wavelength at 485 nM and an emission wavelength at 530 nM. The percent inhibition of a candidate compound at a given concentration is calculated using the following equation:

$$\% \text{ inhibition} = 100 \text{ X} \left\{ 1 - \frac{\text{average OD w/ compound}}{\text{average OD w/o compound}} \right\}$$

and these concentration/inhibition data are used to generate dose response curves, from which IC_{50} values are derived.

The ability of the compounds of this invention to treat arthritis can be demonstrated in a murine collagen-induced arthritis model according to the method of Kakimoto, et al., *Cell Immunol* 142: 326-337, 1992, in a rat collagen-induced arthritis model according to the method of Knoerzer, et al., *Toxicol Pathol* 25:13-19, 1997, in a rat adjuvant arthritis model according to the method of Halloran, et al., *Arthitis Rheum* 39: 810-819, 1996, in a rat streptococcal cell wall-induced arthritis model according to the method of Schimmer, et al., *J Immunol* 160: 1466-1477, 1998, or in a SCID-mouse human rheumatoid arthritis model according to the method of Oppenheimer-Marks et al., *J Clin Invest* 101: 1261-1272, 1998.

The ability of the compounds of this invention to treat Lyme arthritis can be demonstrated according to the method of Gross et al., *Science* 281, 703-706, 1998.

The ability of compounds of this invention to treat asthma can be demonstrated in a murine allergic asthma model according to the method of Wegner et al., *Science*

247:456-459, 1990, or in a murine non-allergic asthma model according to the method of Bloemen et al., *Am J Respir Crit Care Med* 153:521-529, 1996.

The ability of compounds of this invention to treat inflammatory lung injury can be demonstrated in a murine oxygen-induced lung injury model according to the method of Wegner et al., *Lung* 170:267-279, 1992, in a murine immune complex-induced lung injury model according to the method of Mulligan et al., *J Immunol* 154:1350-1363, 1995, or in a murine acid-induced lung injury model according to the method of Nagase, et al., *Am J Respir Crit Care Med* 154:504-510, 1996.

The ability of compounds of this invention to treat inflammatory bowel disease can be demonstrated in a rabbit chemical-induced colitis model according to the method of Bennet et al., *J Pharmacol Exp Ther* 280:988-1000, 1997.

The ability of compounds of this invention to treat autoimmune diabetes can be demonstrated in an NOD mouse model according to the method of Hasagawa et al., *Int Immunol* 6:831-838, 1994, or in a murine streptozotocin-induced diabetes model according to the method of Herrold et al., *Cell Immunol* 157:489-500, 1994.

The ability of compounds of this invention to treat inflammatory liver injury can be demonstrated in a murine liver injury model according to the method of Tanaka et al., *J Immunol* 151:5088-5095, 1993.

The ability of compounds of this invention to treat inflammatory glomerular injury can be demonstrated in a rat nephrotoxic serum nephritis model according to the method of Kawasaki, et al., *J Immunol* 150:1074-1083, 1993.

The ability of compounds of this invention to treat radiation-induced enteritis can be demonstrated in a rat abdominal irradiation model according to the method of Panes et al., *Gastroenterology* 108:1761-1769, 1995.

The ability of compounds of this invention to treat radiation pneumonitis can be demonstrated in a murine pulmonary irradiation model according to the method of Hallahan et al., *Proc Natl Acad Sci U S A* 94:6432-6437, 1997.

The ability of compounds of this invention to treat reperfusion injury can be demonstrated in the isolated rat heart according to the method of Tamiya et al., *Immunopharmacology* 29(1): 53-63, 1995, or in the anesthetized dog according to the model of Hartman et al., *Cardiovasc Res* 30(1): 47-54, 1995.

The ability of compounds of this invention to treat pulmonary reperfusion injury can be demonstrated in a rat lung allograft reperfusion injury model according to the method of DeMeester et al., *Transplantation* 62(10): 1477-1485, 1996, or in a rabbit pulmonary edema model according to the method of Horgan et al., *Am J Physiol* 261(5): H1578-H1584, 1991.

The ability of compounds of this invention to treat stroke can be demonstrated in a rabbit cerebral embolism stroke model according the method of Bowes et al., *Exp Neurol* 119(2): 215-219, 1993, in a rat middle cerebral artery ischemia-reperfusion model according to the method of Chopp et al., *Stroke* 25(4): 869-875, 1994, or in a rabbit reversible spinal cord ischemia model according to the method of Clark et al., *Neurosurg* 75(4): 623-627, 1991.

The ability of compounds of this invention to treat peripheral artery occlusion can be demonstrated in a rat skeletal muscle ischemia / reperfusion model according to the method of Gute et al., *Mol Cell Biochem* 179: 169-187, 1998.

The ability of compounds of this invention to treat graft rejection can be demonstrated in a murine cardiac allograft rejection model according to the method of Isobe et al., *Science* 255: 1125-1127, 1992, in a murine thyroid gland kidney capsule model according to the method of Talento et al., *Transplantation* 55: 418-422, 1993, in a cynomolgus monkey renal allograft model according to the method of Cosimi et al., *J Immunol* 144: 4604-4612, 1990, in a rat nerve allograft model according to the method of Nakao et al., *Muscle Nerve* 18: 93-102, 1995, in a murine skin allograft model according to the method of Gorczynski and Wojcik, *J Immunol* 152 : 2011-2019, 1994, in a murine corneal allograft model according to the method of He et al., *Opthalmol Vis Sci* 35: 3218-3225, 1994, or in a xenogeneic pancreatic islet cell transplantation model according to the method of Zeng et al., *Transplantation* 58:681-689, 1994.

The ability of compounds of this invention to treat graft-vs.-host disease (GVHD) can be demonstrated in a murine lethal GVHD model according to the method of Harning et al., *Transplantation* 52:842-845, 1991.

The ability of compounds of this invention to treat cancers can be demonstrated in a human lymphoma metastasis model (in mice) according to the method of Aoudjit et al., *J Immunol* 161:2333-2338, 1998.

All references cited are hereby incorporated by reference.

The present invention is illustrated by way of the foregoing description and examples. The foregoing description is intended as a non-limiting illustration, since

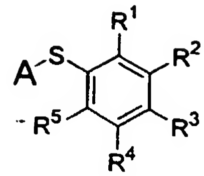
many variations will become apparent to those skilled in the art in view thereof. It is intended that all such variations within the scope and spirit of the appended claims be embraced thereby.

Changes can be made in the composition, operation and arrangement of the method of the present invention described herein without departing from the concept and scope of the invention as defined in the following claims:

CLAIMS

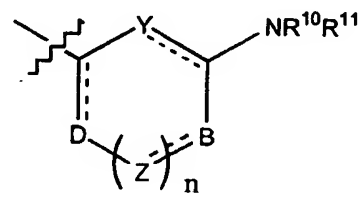
We claim:

1. A compound of the structure



wherein R^1, R^2, R^3, R^4 and R^5 are each independently selected from the group consisting of hydrogen, halogen, alkyl, haloalkyl, alkoxy, cyano, nitro, cycloalkyl and carboxaldehyde;

with the proviso that at least one of R^1 or R^3 is



wherein D, B, Y and Z at each occurrence are independently selected from the group consisting of $-CR^6=$, $-CR^7R^8-$, -C(O)-, -O-, $-SO_2-$, -S-, -N=, and $-NR^9-$;

n is an integer of zero to three;

R^6, R^7, R^8 and R^9, at each occurrence, are each independently selected from the group consisting of hydrogen, alkyl, carboxy,

hydroxyalkyl, alkylaminocarbonyl alkyl, dialkylaminocarbonylalkyl and carboxyalkyl; and

R^{10} and R^{11} are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkoxyalkyl, alkoxycarbonylalkyl, carboxyalkyl, hydroxyalkyl, heterocyclyl, heterocyclylalkyl and heterocyclylamino;

wherein R^{10} and R^{11} may be joined to form a three to seven membered heterocyclyl ring, said ring being optionally substituted with one or more substituents R^{13}, wherein R^{13}, at each occurrence is independently selected from the group consisting of alkyl, alkylene, alkoxy, alkoxyalkyl, cycloalkyl, aryl, heterocyclyl, heterocyclylalkyl, heterocyclylcarbonyl, heterocyclylalkylaminocarbonyl, hydroxy, hydroxyalkyl, hydroxyalkoxyalkyl, carboxy, carboxyalkyl, carboxycarbonyl, carboxaldehyde, alkoxycarbonyl, arylalkoxycarbonyl, aminoalkyl, aminoalkanoyl, aminocarbonyl, carboxamido, alkoxycarbonylalkyl, carboxamidoalkyl, cyano, tetrazolyl, alkanoyl, hydroxyalkanoyl, alkanoyloxy, alkanoylamino, alkanoyloxyalkyl, alkanoylaminoalkyl, sulfonate, alkylsulfonyl, alkylsulfonylaminocarbonyl, arylsulfonylaminocarbonyl and heterocyclylsulfonylaminocarbonyl;

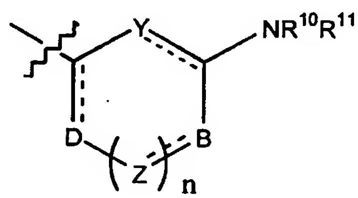
wherein A is an aryl or heterocyclyl group, said aryl or heterocyclyl group having at least one substituent R^{12}, wherein R^{12}, at each occurrence, is independently selected from the group consisting of hydrogen, halogen, alkyl, aryl, haloalkyl, hydroxy, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxyalkoxy, hydroxyalkyl, aminoalkyl,

aminocarbonyl, alkyl(alkoxycarbonylalkyl) aminoalkyl, heterocyclyl, heterocyclylalkyl, carboxaldehyde, carboxaldehyde hydrazone, carboxamide, alkoxycarbonylalkyl, carboxy, carboxyalkyl, carboxyalkoxy, hydroxyalkylaminocarbonyl, cyano, amino, heterocyclylalkylamino, carboxythioalkoxy, carboxycycloalkoxy, thioalkoxy, carboxyalkylamino, trans-cinnamyl and heterocyclylalkylaminocarbonyl; and

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13} are unsubstituted or substituted with at least one electron donating or electron withdrawing group;

or a pharmaceutically-acceptable salt, optical isomer or prodrug thereof.

2. The compound of claim 1 wherein R^3 is



D, B, Y and Z at each occurrence are independently selected from the group consisting of $-CR^6=$, $-CR^7R^8-$, -C(O)-, -O-, $-SO_2-$, -S-, -N=, and $-NR^9-$;

n is an integer of zero to three;

R^6, R^7, R^8 and R^9, at each occurrence, are each independently selected from the group consisting of hydrogen, alkyl, carboxy,

hydroxyalkyl, alkylaminocarbonyl alkyl, dialkylaminocarbonylalkyl and carboxyalkyl;

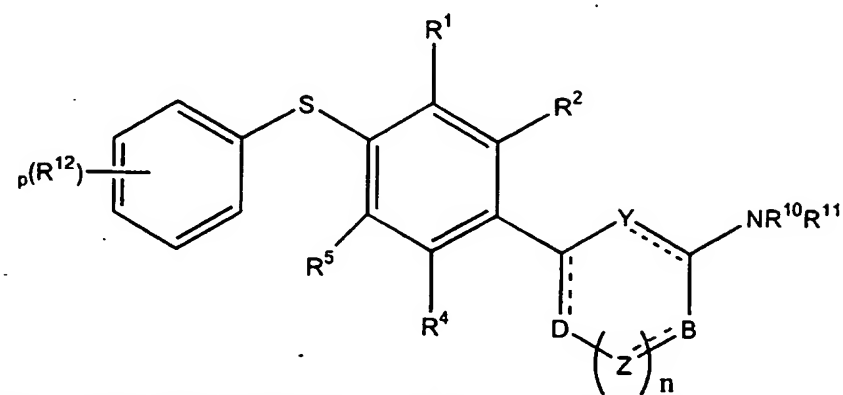
R^{10} and R^{11} are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkoxyalkyl, alkoxycarbonylalkyl, carboxyalkyl, hydroxyalkyl, heterocyclyl, heterocyclylalkyl and heterocyclylamino;

wherein R^{10} and R^{11} may be joined to form a three to seven membered heterocyclyl ring, said ring optionally being substituted with one or more substituents R^{13}, wherein R^{13} at each occurrence is independently selected from the group consisting of alkyl, alkylene, alkoxy, alkoxyalkyl, cycloalkyl, aryl, heterocyclyl, heterocyclylalkyl, heterocyclylcarbonyl, heterocyclylalkylaminocarbonyl, hydroxy, hydroxyalkyl, hydroxyalkoxyalkyl, carboxy, carboxyalkyl, carboxycarbonyl, carboxaldehyde, alkoxycarbonyl, arylalkoxycarbonyl, aminoalkyl, aminoalkanoyl, aminocarbonyl, carboxamido, alkoxycarbonylalkyl, carboxamidoalkyl, cyano, tetrazolyl, alkanoyl, hydroxyalkanoyl, alkanoyloxy, alkanoylamino, alkanoyloxyalkyl, alkanoylaminoalkyl, sulfonate, alkylsulfonyl, alkylsulfonylaminocarbonyl, arylsulfonylaminocarbonyl and heterocyclylsulfonylaminocarbonyl;

R^1 and R^2 are each independently selected from the group consisting of hydrogen, halogen, haloalkyl and nitro; and

R^4 and R^5 are each independently selected from the group of hydrogen and alkyl.

3. The compound of claim 1 of the structure



wherein R^1, R^2, R^4 and R^5 are each independently selected from the group consisting of hydrogen, halogen, alkyl, haloalkyl, alkoxy, cyano, nitro, cycloalkyl and carboxaldehyde;

D, B, Y and Z at each occurrence are independently selected from the group consisting of $-CR^6=$, $-CR^7R^8-$, -C(O)-, -O-, $-SO_2-$, -S-, -N=, and $-NR^9-$;

n is an integer of zero to three;

wherein R^6 , R^7, R^8 and R^9 , at each occurrence, are each independently selected from the group consisting of hydrogen, alkyl, carboxy, hydroxyalkyl, alkylaminocarbonyl alkyl, dialkylaminocarbonylalkyl and carboxyalkyl;

R^{10} and R^{11} are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkoxyalkyl, alkoxycarbonylalkyl, carboxyalkyl, hydroxyalkyl, heterocyclyl, heterocyclylalkyl and heterocyclylamino;

wherein R^{10} and R^{11} may be joined to form a three to seven membered heterocyclyl ring, said ring optionally being substituted with one or more

substituents R^{13}, wherein R^{13} at each occurrence is independently selected from the group consisting of alkyl, alkylene, alkoxy, alkoxyalkyl, cycloalkyl, aryl, heterocyclyl, heterocyclylalkyl, heterocyclylcarbonyl, heterocyclylalkylaminocarbonyl, hydroxy, hydroxyalkyl, hydroxyalkoxyalkyl, carboxy, carboxyalkyl, carboxycarbonyl, carboxaldehyde, alkoxycarbonyl, arylalkoxycarbonyl, aminoalkyl, aminoalkanoyl, aminocarbonyl, carboxamido, alkoxycarbonylalkyl, carboxamidoalkyl, cyano, tetrazolyl, alkanoyl, hydroxyalkanoyl, alkanoyloxy, alkanoylamino, alkanoyloxyalkyl, alkanoylaminoalkyl, sulfonate, alkylsulfonyl, alkylsulfonylaminocarbonyl, arylsulfonylaminocarbonyl and heterocyclylsulfonylaminocarbonyl;

R^{12}, at each occurrence, is independently selected from the group consisting of hydrogen, halogen, alkyl, haloalkyl, alkoxy, carboxyalkoxy, carboxyalkyl and heterocyclyl; and,

p is an integer of zero to five;

wherein R^1, R^2, R^4, R^5, R^{10}, R^{11}, R^{12} and R^{13} are unsubstituted or substituted with at least one electron donating group or electron withdrawing group.

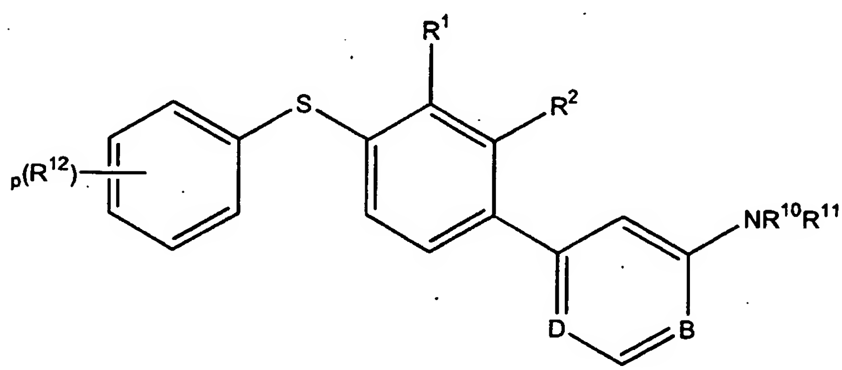
4. The compound of claim 3 wherein p is one;

R^4 and R^5 are hydrogen;

R^{12} is selected from the group consisting of halogen, alkyl, alkoxy, carboxyalkoxy, carboxyalkyl and heterocyclyl; and

R^{10} and R^{11} are joined to form a three to seven membered heterocyclyl ring; said ring selected from the group consisting of piperidine, piperazine, morpholine, pyrrolidine and azetidine.

5. The compound of claim 1 of the structure



wherein D and B are each independently selected from the group consisting of –N= and –CR^6=;

R^1 and R^2 are each independently selected from the group consisting of hydrogen, halogen and haloalkyl;

R^{10} and R^{11} are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkoxyalkyl, alkoxycarbonylalkyl,

carboxyalkyl, hydroxyalkyl, heterocyclyl, heterocyclylalkyl and heterocyclylamino;

wherein R^{10} and R^{11} may be joined to form a three to seven membered heterocyclyl ring, said ring optionally substituted with one or more substituents R^{13}, wherein R^{13} at each occurrence is independently selected from the group consisting of alkyl, alkylene, alkoxy, alkoxyalkyl, cycloalkyl, aryl, heterocyclyl, heterocyclylalkyl, heterocyclylcarbonyl, heterocyclylalkylaminocarbonyl, hydroxy, hydroxyalkyl, hydroxyalkoxyalkyl, carboxy, carboxyalkyl, carboxycarbonyl, carboxaldehyde, alkoxycarbonyl, arylalkoxycarbonyl, aminoalkyl, aminoalkanoyl, aminocarbonyl, carboxamido, alkoxycarbonylalkyl, carboxamidoalkyl, cyano, tetrazolyl, alkanoyl, hydroxyalkanoyl, alkanoyloxy, alkanoylamino, alkanoyloxyalkyl, alkanoylaminoalkyl, sulfonate, alkylsulfonyl, alkylsulfonylaminocarbonyl, arylsulfonylaminocarbonyl and heterocyclylsulfonylaminocarbonyl;

R^{12}, at each occurrence, is independently selected from the group consisting of hydrogen, halogen, alkyl, haloalkyl, alkoxy, carboxyalkoxy, carboxyalkyl and heterocyclyl; and,

p is an integer of zero to five;

wherein R^1, R^2, R^{10}, R^{11}, R^{12} and R^{13} are unsubstituted or substituted with at least one electron donating group or electron withdrawing group.

6. The compound of claim 5 wherein p is one;

R^{12} is selected from the group consisting of halogen, alkyl, alkoxy, carboxyalkoxy, carboxyalkyl and heterocyclyl; and

R^{10} and R^{11} are joined to form a three to seven membered heterocyclyl ring; said ring selected from the group consisting of piperidine, piperazine, morpholine, pyrrolidine and azetidine.

7. The compound of claim 1 selected from the group consisting of 1-(6-(4-(2-isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-yl)-piperidine-3-carboxylic acid, 4-(4-(2-isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-6-(3-(2*H*-tetrazol-5-yl)-piperidin-1-yl)-pyrimidine, 4-(4-(2-isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-6-(4-(2*H*-tetrazol-5-yl)-piperidin-1-yl)-pyrimidine, (1-(6-(4-(2-isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-yl)-piperidin-3-yl)-methanol, 2-(1-(6-(4-(2-isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyrimidin-4-yl)-piperidin-4-yl)-ethanol, *N*-(1-(4-(4-(2-isopropyl-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-pyrrolidin-3-yl)-acetamide, 1-(4-(4-(2-methoxy-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-pyrrolidine-3-ol, *N*-1-(4-(4-(2-methoxy-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-pyrrolidine-3-yl)-acetamide, *N*-1-(4-(4-(2-methoxy-phenylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-pyrrolidine-3-yl)-acetamide, *N*-(1-(4-(4-(2,3-dihydro-

benzo(1,4)dioxin-6-ylsulfanyl)-3-trifluoromethyl-phenyl)-pyridin-2-yl)-pyrrolidin-3-yl)-acetamide, 4'-(4-(2,3-dihydro-benzo(1,4)dioxin-6-ylsulfanyl)-3-trifluoromethyl-phenyl)-3,4,5,6-tetrahydro-2*H*-(1,2')bipyridinyl-4-carboxylic acid and 4'-(4-(2,3-dihydro-benzo(1,4)dioxin-6-ylsulfanyl)-3-trifluoromethyl-phenyl)- 3,4,5,6-tetrahydro-2*H*-(1,2')bipyridinyl-3-carboxylic acid.

8. A composition comprising:

a compound of claim 1

in a pharmaceutically acceptable carrier.

9. A method of inhibiting inflammation or suppressing immune response in a mammal comprising administering to said mammal a therapeutic amount of a compound of claim 1.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/20128

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D263/48 C07D277/42 C07D239/42 C07D403/12 C07D401/04
C07D403/04 C07D401/14 A61K31/425 A61K31/505
//(C07D403/12,239:00,233:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 262 845 A (FISONS PLC) 6 April 1988 (1988-04-06) page 8, line 30 -page 9, line 3; claims; examples 3K,5J,5K ---	1-9
Y	DATABASE WPI Week 199642 Derwent Publications Ltd., London, GB; AN 1996-425115 XP002180199 -& WO 96 26921 A (TOYAMA CHEMICAL CO. LED.;CHAKI HISAAKI (JP); KURODA HIROSHI (JP);M)), 6 September 1996 (1996-09-06) abstract ---	1-9
A	AT 392 788 B (FISONS PLC.) 10 June 1991 (1991-06-10) page 7, line 37 - line 45; claims ---	1-9

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 October 2001	31/10/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Frelon, D

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	EP 0 455 356 A (LILLY INDUSTRIES LTD) 6 November 1991 (1991-11-06) page 6, line 25 - line 29; claims	1-9
A	EP 0 710 654 A (GREEN CROSS CORP) 8 May 1996 (1996-05-08) abstract; claims	1-9
A,P	EP 1 052 238 A (SHIONOGI & CO) 15 November 2000 (2000-11-15) page 194, line 19 - line 21; claims	1-9
A,P	WO 00 39081 A (ABBOTT LAB) 6 July 2000 (2000-07-06) the whole document	1-9
A,P	WO 00 59880 A (ABBOTT LAB) 12 October 2000 (2000-10-12) the whole document	1-9

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims relate to an extremely large number of possible compounds because of the lack of specification of terms like alkyl, aryl, heterocyclyl, etc, derivatives thereof and other unspecified terms like "electron donating", "electron withdrawing" or "prodrug". Such terms render the subject-matter unclear to such an extent that a meaningful search of the claims is not possible. The matter for which protection is sought is not properly defined. Moreover, the terms "electron donating", "electron withdrawing" and "prodrug" cannot be considered to be supported by the definition since the appropriate passages of the description (pages 17 and 15-16, resp.) only give general definitions. No example is disclosed.

Consequently, the search has been carried out for those parts of the application which do appear to be clear, i.e. to the extent that the disputed terms may be covered by the definition of the remaining part of the Markush formula.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

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